Comparative Physiology of the Thyroid and Parathyroid Glands

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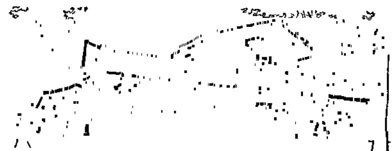
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Comparative Physiology of the Thyroid and Parathyroid Glands

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CHAPTER I

Introduction

"PALEO-ENDOCRINOLOGY and comparative endocrinology, particularly in their biochemical aspects may broaden our understanding of man's endocrine systems as they are today" (Means, 1947). It is encouraging for the comparative physiologist to find a statement like this in the most recent edition of a standard text on clinical endocrinology. The present lecture is an attempt to review our knowledge of the comparative endocrinology of the thyroid and parathyroid glands.

Paired entodermal protuberances are formed in all vertebrates during early embryonic life at the cranial end of the gut. These protuberances, the gill pouches, are connected with protrusions of the ectoderm, the gill furrows. The derivates of these structures are designated as branchiogenic organs. These include the thyroid and parathyroid glands and the thymus. The function of the latter is obscure. The thyroid and parathyroid glands can thus be grouped together anatomically because of their common developmental origin (Grollman, 1947). Physiologically, however, they are entirely independent from each other and no functional relationship has been demonstrated. Both organs are exclusively confined to the vertebrate phylum It seems reasonable to assume that the effects of the hormones of these glands are restricted to this phylum. This is borne out by the negative results of experiments on the effects of administration of mammalian thyroid hormone

to invertebrates. For instance, the administration of thyroxin was found to be without effect on the metamorphosis of insects (Fleischmann, 1929). A review of the pertinent literature reveals that all efforts have failed to demonstrate an unequivocal effect of the thyroid hormone on invertebrates.

No work seems to have been done on the effects of administration of parathyroid hormone on invertebrates.

CHAPTER II

Tunicates and Acraniates

THE ENDOSTYLE found in the lowest chordate animals—tunicates and acraniates—was long believed to be homologous and analogous to the vertebrate thyroid gland. This idea has been discarded more recently for morphological reasons (Hyman, 1942) and because of the fact that neither the endostyle of the tunicate, *Perophora annectens* (Gorbman, 1941), nor that of the acraniate, *Amphioxus* (Gorbman and Greaser, 1942), is capable of storing radioactive iodine. In view of these facts it is not surprising that the endostylar tissue of the tunicate *Ciona intestinalis* contains no factor capable of inducing metamorphosis in tadpoles (Spaul, 1928).

CHAPTER III

Fish

In contrast to the endostyle of the tunicates and acraniates the endostyle of the larvae of the most primitive fish, the lamprey, has a definite relationship to the thyroid gland encountered in higher forms. The larval form of all lampreys is known as the "ammocoete" stage. The nomenclature is somewhat confusing because early naturalists regarded Ammocoetes as an adult cyclostome and classified it as a distinct genus. The thyroid gland of the adult lamprey consisting of isolated follicles represents the most primitive anatomical condition of the gland (Leach, 1946; Goldsmith, 1949). The theory that the endostyle in the larval or ammocoetes stage is a primitive thyroid mechanism concerned with iodine metabolism has recently been corroborated through studies using radioactive iodine (I^{131}) as a tracer. Specific cells of the endostyle of ammocoetes of the free-living lamprey *Entospenus lamottenii* are capable of storing radioactive iodine. It seems significant that endostylar tissue actively removes inorganic iodine from its fluid environment and stores it intracellularly even before it has begun its definite differentiation into thyroid tissue (Gorbman and Creaser, 1942). Metamorphosis from the larval or ammocoetes stage to the lamprey is not accompanied by an increase in oxygen consumption. It has been further shown that ammocoetes larvae do not respond to administration of mammalian thyroid. Neither the rate of metamorphosis nor that of metabolism is affected. The theory

has been proposed that the thyroid in the lowest vertebrates is concerned mainly with growth and maturation (Leach, 1946).

In most fish the thyroid consists of follicles scattered in the connective tissue along the ventral aorta and afferent branchial arteries. This anatomical distribution precludes surgical thyroidectomy in fish. Before the introduction of anti-thyroid drugs no work could be done on experimental thyroid deficiency in fish. However, some species of teleosts have a discrete, compact thyroid gland In one of these, the Bermuda parrot fish, *Sparisoma sp.*, concentration of radioactive iodine in the compact thyroid gland has been demonstrated (Matthews and Smith, 1948).

The problem of metamorphosis in fish is a very complex one. Sklower (1928) and Hagen (1936) described marked hyperplasia of the thyroid in the larvae of the eel at the time of transformation from leptocephalus to elver. A similar change occurs in the thyroid of the flatfish, *Pleuronectes platessa*, during metamorphosis (Sklower, 1930). In a tropical goby, *Periophthalmus chrysospilos*, metamorphosis can be accelerated by thyroid feeding. It is of interest that these fish normally lead an amphibian life. After administration of desiccated thyroid they live less in the water and more on land than the untreated controls A blenny from the Adriatic sea, *Blennius ocellatus*, was induced to lead an amphibian life by feeding it mammalian thyroid hormone (Harms, 1929) although this species is usually strictly aquatic

Robertson (1948) made a careful study of the color transformation and the associated changes in the secretory activity of the thyroid gland which young rainbow trout in certain Michigan streams exhibit before migrating into one of the Great Lakes The change of color was found to be due principally to the deposition of a greatly increased

amount of guanine on the internal surface of the scales, laid down as crystals. This accounts for the silvery color of the smolt (second year fish) in comparison to the darker color of the parr (first year fish). Examination of the thyroid gland of the smolt revealed increased functional activity as compared with the thyroid of the parr. The transformation from parr to smolt is accompanied by change from a cuboidal to a columnar type of follicular epithelium and vacuolization and loss of colloid from the lumen of the follicles. Measurements of the height of the follicular epithelium confirmed the impression of hyperactivity of the thyroid in the recently transformed smolt.

Similar changes have been observed in the salmon, *Salmo salar*. The young salmon has a moderately active gland. After their return to fresh water, these young salmon (smolts) show a very active thyroid as judged by its histological appearance. In the adult functional activity decreases again and attains its lowest level at the time of spawning. There is a new phase of activity when the salmon returns to the sea for the second time (Fontaine and Olivereau, 1947).

Surgical removal of the thyroid tissue has never been accomplished in fish because of the anatomical distribution mentioned above. However, "chemical thyroidectomy" (see below) has yielded interesting results. Goldsmith *et al.* (1944) immersed fish in solutions of the anti-thyroid drug, thiourea. This drug produces hypothyroidism through inhibition of the synthesis of the normal thyroid hormone. A hybrid strain involving *Platypoecilus maculatus* and *Xiphophorus helleri* was used. A marked inhibition of growth was noted in the fish exposed to thiourea. This was not due to inanition, since the animals accepted food as readily as did the untreated controls. A histological examination of the thyroid tissue of the

thiourea-treated animals, as compared with the controls, showed a very definite hyperplasia.

Most fish are very insensitive to thyroxin. Root and Etkin (1937) found that thyroxin injected through four to five days in doses of 10 mg. per kg. bodyweight had no effect on the oxygen consumption of the toadfish, *Opsanus tau*. However, the oxygen consumption of the same fish could be increased by injection of dinitrophenol in doses of 7 mg. per kg. bodyweight. Smith and Everett (1943) confirmed the opinion that thyroid preparations fail to enhance oxygen consumption or somatic growth in the fish, *Lebistes reticulatus*.

In the brook trout, *Salvelinus fontinalis*, hyperplasia of thyroid tissue has been studied by Marine and Lenhart (1910, 1911). Extensive formation and spreading of new follicles were observed. This condition is comparable to endemic goiter in human beings. Over-feeding and overcrowding are important factors associated with the development of thyroid hyperplasia. Prevention and cure is favored by adjusting the amount of food and the number of fish to the water supply and by the addition of iodine-containing substances to the water.

No parathyroid tissue has been found in fish.

CHAPTER IV

Amphibia

AN OBSERVATION of Gudernatsch (1913) led to the development of a new field in experimental biology. He found that a diet of mammalian thyroid administered to tadpoles of frogs led to the onset of metamorphosis within a few days. Thyroid administered at any age after the tadpole was capable of taking solid food had this effect. The time at which the feeding began did not influence the result. If the treatment began early, the tadpoles fed on a thyroid diet underwent precocious metamorphosis with remarkable uniformity weeks before the controls fed on other tissues. The individuals of a thyroid-fed group in all cases transformed within about a day of one another. No such uniformity is seen in normal tadpoles nor in the control tadpoles fed by Gudernatsch on other tissues. Gudernatsch used the European species, *Rana esculenta* and *Rana temporaria*. *Swingle (1918) confirmed those results* on the American bullfrog, *Rana catesbiana*. In a state of nature it requires two or three seasons for the tadpoles of this species to attain the adult condition, and the gonads contain ripe germ cells long before the onset of metamorphosis. Swingle (1918) fed desiccated mammalian thyroid to tadpoles of the bullfrog, *Rana catesbiana*, shortly after hatching. Within three weeks after hatching he had produced miniature frogs having all the bodily characteristics of the adult with the exception of the gonads which remained immature.

The effect of thyroid hormone on amphibian metamorphosis can be used for the bio-assay of thyroid preparation. For this purpose the eruption of the fore-limbs in tadpoles of *Xenopus laevis* has proved to be the most satisfactory end-point (Hamilton *et al.*, 1948).

It is not our aim to review all papers dealing with thyroid-induced metamorphosis in amphibians but to confine ourselves to work that sheds light on the mechanism of thyroid action or that contributes to comparative physiology.

It has been observed by a number of workers that the induction of metamorphosis by thyroid hormone in tadpoles is accompanied by a marked increase in oxygen uptake (Helff, 1926). Abelin and Scheinfinkel (1923) reported an initial slight rise in total CO_2 production in tadpoles of *Rana esculenta* fed with thyroid tissue. The rise was followed by a decrease in CO_2 production during metamorphosis. On the basis of these and similar data, Hogben (1929) suggested "that the histogenic incidents of metamorphosis are a consequence of the increased oxidative activity in the tissue." This problem has been reinvestigated by Etkin (1934), who made careful measurements of the oxygen consumption of tadpoles of the bullfrog, *Rana catesbiana*, in relation to the various stages of normal metamorphosis. Etkin feels that there is at present no reason for ascribing any causative significance in metamorphosis to the stimulating influence of thyroid hormone on metabolism. We agree with this conclusion because of studies on the effect of dinitrophenol on tadpoles. This compound is known to enhance metabolism through the increase of tissue oxidations Cutting and Tainter (1933) found no influence of this substance on the metamorphosis of the toad, *Bufo halophilus*, using a wide range of concentrations up to toxic doses; their negative results were

confirmed by the author. It is probable, however, that there is a difference in the mechanism of action of thyroxin and of dinitrophenol on tissue oxidations and that, therefore, the stimulating action of these compounds on oxygen uptake is not strictly comparable.

The study of the chemical changes in the body of amphibians undergoing spontaneous or induced metamorphosis should be of great interest to the investigators in the field of developmental physiology. Few data are available at the present time, however. Haffner (1927) found an increased content of lactic acid in the body of tadpoles treated with thyroxin. Nagel (1927) studied the initial water loss of the axolotl after thyroid administration. He felt that this water loss is a causative factor in inducing metamorphosis. Feeding of thyroid substance to tadpoles induces an increase in oxygen uptake whereas the basal metabolic rate of adult frogs is not affected by thyroid administration (Helff, 1923). Thyroxin has no influence on the metabolism of the intact or thyroidectomized frog, *Rana esculenta*. Thyroidectomy did not depress the basal metabolic rate of adult specimens of this frog (Henschel and Steuber, 1931).

Champy (1922) made mitotic counts in various regions of the body during thyroid-induced metamorphosis in tadpoles of the frog, *Rana temporaria*. The epidermis of the bud of the fore-limb reacts to the thyroid hormone by an increase in mitotic activity, the lining of a branchial cleft (gill) by degeneration as manifested by shrunken nuclei and vacuolization of the cytoplasm. There is no transitional region between these two types of histological response. It seems probable that the orderly succession of steps in metamorphosis is due to a series of threshholds of response. The threshhold for the hormone is lowest in the epidermis according to Drzewicki (1924). Minute

amounts of thyroid were fed to larvae of the toad, *Pelobates fuscus*. The epidermis was the only tissue in which mitotic activity and differentiation could be observed.

Nutritional factors influence the rate of induced metamorphosis. The thyroxin-induced metamorphosis of the larvae of *Salamandra maculosa* was retarded by feeding of vitamin A in olive oil. The controls were fed with olive oil only (Fleischmann and Kann, 1937).

The operative removal of the thyroid gland of amphibian embryos was first carried out on tadpoles of the frog, *Rana pipiens* (Allen, 1917). No peculiarities attributable to the operation were detected until about three months after the thyroid anlage had been destroyed. At this time the tadpoles failed to undergo metamorphosis, while growth continued and the gonads proceeded to develop. The brain and alimentary tract retained, along with the general configuration, the larval characteristics. The vertebrae developed no spinous processes and remained unossified, though extensive calcification occurred. Deposition of lime salts went on, but the stimulation to the proliferation of the odontoblasts was lacking.

The discovery that certain sulfur-containing drugs cause a marked hyperplasia of the thyroid gland (MacKenzie *et al.*, 1941; Richter and Clisby, 1942) led to the development of valuable tools for the study of thyroid physiology. The MacKenzies (1943) and Astwood *et al.* (1943) elucidated the mechanism of this action by showing that hyperplasia is prevented by administration of thyroid hormone and that it is associated with a fall in the basal metabolic rate. The effect on the basal metabolic rate can be neutralized by the administration of thyroid hormone concurrently with the anti-thyroid drug. In hypophysectomized animals the anti-thyroid drugs produce no hyperplasia of the thyroid gland. These facts

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prove that the anti-thyroid drugs act through inhibition of the formation of the thyroid hormone by the gland. The thyroid hyperplasia is probably compensatory for the lack of synthesis of the thyroid hormone. Lack of circulating thyroid hormone acts as a stimulus to the anterior lobe of the pituitary gland which responds with increased production of thyrotrophic hormone. This hormone is, therefore, responsible for the hyperplasia of the thyroid.

Thiouracil, a derivative of thiourea, is used most commonly for experiments on the chronic inhibition of the formation of the thyroid hormone, or "Chemical thyroidectomy" because of its low toxicity. The inhibition of amphibian metamorphosis by thiourea was first demonstrated by Gordon, Goldsmith and Charipper (1943). They used tadpoles of the frog, *Rana pipiens*. As a result of treatment with thiouracil metamorphosis was inhibited, but growth continued. Giant tadpoles were obtained, whose thyroid gland showed morphological signs of activation. Hughes and Astwood (1944) studied the inhibitory effect of thiouracil dissolved in the culture medium on tadpoles of the frog, *Rana clamitans*. Normal metamorphosis was inhibited by concentrations of 1:8000. The rate of metamorphosis induced by thyroxin was not changed by the presence of thiouracil in a concentration of 1·2000. This is understandable if we assume that thiouracil inhibits the production of endogenous thyroid hormone, but does not interfere with the action of exogenous hormone. The effectiveness of thiouracil as an inhibitor of hormone production was demonstrated also by experiments on tadpoles injected with the thyrotrophic hormone of the pituitary. While tadpoles living in water and receiving thyrotrophic hormone of the pituitary were completely metamorphosed in 13 to 19 days, tadpoles living in a 1:2000 solution of thiouracil and receiving thyro-

trophic hormone did not metamorphose. Goldsmith, Gordon and Charipper (1943) studied the effect of thiourea on the metamorphosis of *Rana pipiens* and came to the same conclusion. They have very clearly demonstrated the reversibility of the thiourea effect. Development of frog larvae can be kept in complete abeyance by immersion of the larvae in a solution of thiourea. Signs of resumed metamorphosis are displayed very early following discontinuance of treatment, provided the immersion is not continued for too long a time. Thiourea was given to tadpoles of *Rana catesbiana* during the proliferative phase of tail regeneration following amputation of the tail. This resulted in a retardation of the rate of growth of the new tail (Ghidoni, 1948). The thyroid glands of tadpoles of the frog, *Rana esculenta,* were transplanted into tadpoles of the same species. Young tadpoles with a length of the hind legs of 8 mm. were used as hosts. If thyroid glands of tadpoles of the same age were implanted no effect could be observed on metamorphosis or on the thyroid gland of the host. If older tadpoles were used as donors the metamorphosis of the host was accelerated and the development of the thyroid of the host was markedly retarded. These findings suggest that the thyroid of the young tadpole contains less hormone than that of the tadpole in the stage in which it undergoes complete metamorphosis (Slowikowska, 1923). Sklower (1925) studied the thyroid histology of tadpoles of the frog, *Rana temporaria,* during various stages of development. The greatest activity, as judged from the histological appearance, was observed in thyroids of tadpoles in the final stages of metamorphosis.

Radioactive iodine has been used with great success in developmental studies. Tadpoles of the frog, *Hyla regilla,* which ranged in size from freshly hatched larvae

7 mm. in length to larvae 38 mm. in length with developed hind legs, were maintained for two days in 800 ml. water which contained 150 microcuries of I^{131}. The tadpoles were fixed and sectioned at the end of two days. Radioautographs were made from these sections, which were later stained with hematoxylin and eosin. No evidence of storage could be found in larvae less than 10 mm. in length. The first deposition of I^{131} was noted in the 10 mm. larvae, that is soon after completion of the embryonic tail-bud stage. Developmental changes in the histological picture of later stages of the tadpole were accompanied by an increased ability of the thyroid to accumulate labeled iodine (Gorbman and Evans, 1941a).

In order to test the relation of the thyroid to different stages of metamorphosis, the thyroid anlage of tadpoles was transplanted from its normal situation to the tail. Thus the gland could be removed at appropriate intervals after the onset of changes. After the legs were well developed, subsequent removal of the thyroid did not prevent the completion of metamorphosis. If the gland were removed prior to the development of the legs, metamorphosis was incomplete (Hoskins, 1922).

The relationship of the thyroid to molting has been examined in the newt *Triturus viridescens* (Adams, Richards and Kuder, 1930). Thyroidectomy inhibits shedding of the skin. The animals lacking thyroid became gradually blacker, as layer after layer of cornified cells were formed and not sloughed off. Thyroid glands of normal newts transplanted into thyroidectomized animals will induce a complete molt of the many-layered epidermis.

Neoteny is the retention of the larval form beyond the normal time required for metamorphosis. Partial neoteny is quite common in some frogs such as *Rana catesbiana.* Tadpoles of this species often retain their larval form

far beyond the normal time required for metamorphosis but finally undergo complete metamorphosis spontaneously. In total neoteny the animal retains its gills and other larval characteristics permanently, becoming sexually mature in this condition. The classical example of total neoteny is the axolotl larva of the Mexican salamander, *Amblystoma mexicanum*. The larva never undergoes metamorphosis spontaneously. Axolotls may live for 10 years, breeding in captivity from generation to generation in the larval state. It was shown by Babak in 1913 that a single meal of mammalian thyroid suffices to induce metamorphosis. The first shedding of the larval skin takes place about 9 to 13 days later, and metamorphosis is practically complete within four to six weeks.

The case of the axolotl raised the possibility that the perennibranchiate genera — *Proteus*, *Necturus* and *Typhlomolge* — may in reality be sexually mature larval forms with a deficiency of the endocrine mechanism responsible for metamorphosis. Of these urodeles, *Proteus anguineus* and *Necturus maculatus* have thyroid glands. By grafting the thyroids of *Necturus maculatus* into bullfrog larvae, Swingle (1922) showed that they contained a substance capable of inducing metamorphosis of the bullfrog larvae, *Rana catesbiana*. Prolonged thyroid feeding has no effect on *Proteus* or *Necturus* (Hogben, 1929). The extreme case is that of *Typhlomolge rathbuni* in which the thyroid seems to be congenitally lacking (Swingle, 1922).

There has been much speculation as to the cause of the failure of neotenous amphibia to undergo metamorphosis. In the case of the axolotl it may be that the amount of thyroid hormone produced by the animals own gland is too small to induce the specific changes in the tissues. There is suggestive evidence for this in the work of Rolic (1927) who induced metamorphosis of an axolotl by transplant-

ing many thyroid glands of the same species. In the perennibranchiate the tissues have apparently lost the faculty to respond to thyroid hormone.

In the urodeles which always undergo metamorphosis spontaneously, such as *Triton alpestris* or *Salamandra maculosa*, metamorphosis can be accelerated through thyroid feeding (Kuhn, 1925). A synopsis of the findings on Urodeles is given in Table I (from Fleischmann, 1947).

The parathyroids in *Rana catesbiana* are commonly four in number and are not in close proximity to other endocrine glands. An operative technique of complete parathyroidectomy was developed for this species. Removal of the gland was followed by a short period of apparent normality. Hyperexcitability followed, and then violent contractions involving large muscles or groups of muscles occurred. These neuromuscular disturbances would sometimes develop into a typical tetany, in other cases, tremors and twitchings of a less severe nature followed. This hyperactive phase was followed by a state of inactivity, which was probably due to an increased tonus

TABLE I

THYROID PHYSIOLOGY IN URODELES

SPECIES	THYROID GLAND ACTIVITY AS DEMONSTRATED			
	By Histology	By Bio-assay*	METAMORPHOSIS SPONTANEOUS	INDUCED BY THYROID FEEDING
Triton alpestris	+++	++	+	+
Salamandra maculosa	+++	++	+	+
Amblystoma mexicanum	+	+	0	+
Proteus anguineus	+	−	0	0
Necturus maculatus	+	+	0	0
Typhlomolge rathbuni	Thyroid absent		0	−

* The activity was estimated by the effect of the transplanted glands on the metamorphosis of tadpoles

of muscles and finally culminated in the onset of a deep depression and death about three days after operation. Calcium levels dropped from 11.5 to 7.7 mg. per 100 ml. of whole blood after parathyroidectomy (Waggener, 1930).

CHAPTER V

Reptiles

LITTLE WORK has been done on thyroid physiology in this class of vertebrates. Noble and Bradley (1933) have studied the effect of thyroidectomy on molting in the lizard, *Hemidactylus brookii.* Thyroidectomy lengthens the periods between molting, but never prevents molting entirely. Injections of thyroxin bring a return of the molt to its normal periodicity. However, neither injections of thyroxin nor implantations of fresh lizard thyroid increase the frequency of molt in the intact lizard. Eggert (1933) has studied the correlation between the histological changes and molting in lizards of the genus *Lacerta.* He finds that the thyroid undergoes cyclic changes parallel to those of the skin. At the time of shedding of the old skin, the thyroid is comparatively inactive. The onset of maximal activity coincides with the fourth or fifth day after molting. Atrophy of the ovaries as a result of the administration of thyroxin has been described in the horned lizard, *Phrynosoma cornutum* (Mellish and Meyer, 1937). Transformation of the chromophobic cells of the anterior pituitary into basophilic cells has been observed after thyroidectomy in the garter snake, *Thamnophis radix* (Siler, 1936).

CHAPTER VI

Birds

THE ADMINISTRATION of exogenous thyroid hormone has a marked effect on the plumage of birds. Mammalian thyroid hormone given orally or thyroxin injected intramuscularly results in molting, accelerated regeneration of feathers and changes in the pattern and structure of regenerated feathers. Not all species of birds are equally sensitive. Domesticated birds, such as chickens and pigeons, are more sensitive to exogenous thyroid hormone than wild birds, such as the common crow, *Corvus corone*. Even large doses of thyroid do not produce any molting in crows, although considerable depigmentation of feathers occurs (Zawadowsky and Rochlina, 1927).

Synergistic action of the thyroid hormone and of the androgens has been observed in birds. Pigment deposition in the grey breast feathers of the Mallard drake is conditioned both by androgens and by thyroid hormone. Treatment with thyroid hormone resulted in pigment deposition in the normal adult drake, but is without effect in the castrate (Jaap, 1934). In order to obtain the same increase in the size of the comb, a greater amount of androgen must be given to thyroidectomized than to non-operated control capons (Caridroit and Regnier, 1941).

The mechanism of action of thyroxin on the plumage has been studied by Lillie and Juhn (1932). They injected thyroxin into fowl at definite time intervals after plucking. In this way, regenerating feathers of known age were ex-

posed to the hormone, and a record was obtained in the definitive feather of the physiological events taking place during its formation from the feather germ. The saddle feathers of the Brown Leghorn male were used in this work. Following the injection of thyroxin, barbules were formed in regions normally free of barbules. With increasing doses of thyroxin, black pigment appeared. Barbule formation and pigment deposit followed each other in order of increasing thyroxin concentrations. Barbule formation may occur alone, but pigment formation is always associated with barbule formation.

Parkes and Selye (1937) were the first to observe that thyroidectomy in fowl is followed by loss of barbules, leading to fringing and elongation of the feather in relation to width.

Blivaiss (1947) has studied the effects of complete thyroidectomy on Brown Leghorns which had undergone thyroid removal on the fourth to twentieth day after hatching. Thyroidectomy delays the appearance of definitive feathers, juvenile feathers in all regions persisting longer than normal. Juvenile feathers show a decrease in melanin and barbules and an increase in red pigment. In the adult thyroidectomized rooster, body contour feathers show a loss of melanin, which is replaced by a red pigment. Loss of melanin is associated with loss of sheen. These feathers also show a decrease in the number of their barbules, resulting in a hackled, fluffy appearance and a tendency to become elongated, narrow and tapered. In the thyroidectomized hen, the contour feathers show the same type of modification as do the feathers of the thyroidectomized rooster. A striking similarity of the breast feathers is observed in both sexes, both the black color of the male and the salmon color of the female being replaced by red pigment.

Thiouracil has the same effect on the plumage of the Brown Leghorn capon as thyroidectomy. Black pigment is replaced by red pigment. After discontinuing the drug, black pigment reappears (Juhn, 1944). Brown Leghorn chicks were treated with the anti-thyroid drug, thiouracil, starting at the age of seven weeks. At a period when controls were in full adult plumage, the treated roosters showed red feather pigments and reduced barbulation with an associated feather elongation in place of solid black contour feathers (Juhn, 1947). According to Sulman and Perek (1947), thiouracil feeding in White Leghorn hens diminishes the basal metabolic rate but does not affect molting.

Brown Leghorn males suffering from leucosis show a characteristic change to red in the black plumage tracts of their bodies. Thyroxin causes a return to black in such abnormal feathers (Juhn, 1942).

The effect of thyroid deficiency in chicks has been studied with the aid of thiouracil (Astwood, Bissell and Hughes, 1944). One-tenth of one per cent thiouracil in the food induced maximal enlargement and hyperplasia of the thyroid gland and a decrease in its iodine content. When given as a 0.5 per cent mixture in the food, growth and development were markedly retarded; wattles, comb and spurs failed to develop, muscles were weak, joints hypermobile, and finally the chicks were unable to stand. A fringe of wing feathers grew during the first few weeks, but the down persisted and body feathers did not appear. This condition was interpreted as a state of cretinism. The amount of thyroxin necessary to keep the thyroid weights of thiouracil-fed male chicks at normal levels was determined by Mixner, Reineke, and Turner (1944). The average daily output of the thyroid was estimated at about two to three micrograms of thyroxin per day up to the

age of 14 days. Feeding of thiouracil to hens leads to thyroid enlargement in their chicks. This proves that thiouracil is transmitted through the egg (Andrews and Schnetzler, 1945).

Surgical thyroidectomy in mature fowl severely reduces egg production which may be restored by feeding of desiccated thyroid (Winchester, 1939). Winchester and his associates (1949) have recently destroyed the thyroid gland by injection of radioactive iodine (I^{131}). Chicks were injected at the age of three weeks with a dosage of from 30 to 90 millicuries per kg. bodyweight; they grew very slowly and survived only a limited time after injection unless they were given desiccated thyroid by mouth. Growth and feather development were quickly resumed after the initiation of thyroid treatment. The rates of egg production of hens "radio-thyroidectomized" with I^{131} and given substitution therapy with desiccated thyroid was excellent.

Anti-thyroid drugs — thiourea or thiouracil — have been injected into incubating eggs. The main effects were retardation of hatching and lack of retraction of yolk sac. The growth of the chick embryo was retarded. The embryonic thyroid was enlarged with typical hyperemia hyperplasia and hypertrophy. The follicular epithelium was increased in height (Adams and Bull, 1949).

Antagonistic action of exogenous thyroxin and exogenous estradiol was observed in chickens (Fleischmann and Fried, 1945). Thyroxin when administered simultaneously and in equal amounts with estradiol dipropionate in immature chicks, inhibits the ability of the estrogen to increase the plasma calcium, inorganic phosphorus, protein phosphorus, lipid phosphorus, and cholesterol, but does not inhibit the growth of the oviduct. In pigeons, thyroxin was observed to inhibit estrogen induced changes in the

plasma levels of calcium, neutral fat, and all phosphorus fractions, without inhibiting the action of estrogen on the formation of endosteal bone and promotion of the growth of the oviduct (McDonald, Riddle and Smith, 1945). The estrogen-induced changes in the plumage of Brown Leghorn capons are not modified by the simultaneous administration of thyroxin (Caridroit, 1940; Fleischmann, 1946). These findings indicate that the inhibiting effect of thyroxin is confined to metabolic changes, whereas the structural changes brought about by the estrogen are not affected.

A condition in fowl comparable to sporadic cretinism in human beings was described by Landauer (1929). He made careful anatomical studies of a dwarfed Rhode Island Red pullet. The bird exhibited a general arrest in growth, a striking brachycephaly, and myxedematous swelling of the skin. The skin was dry. Measurements of the skeleton showed marked deviation from the normal, similar to those found in human cretins. Endochondral ossification was suppressed. The thyroid was enlarged and the greater part of the gland consisted of entirely aplastic tissue without any colloid. In pigeons the basal metabolic rate is depressed after removal of the thyroid. One week after operation the basal metabolic rate was 20 per cent lower than in the control birds (Marvin and Smith, 1943).

Removal of the parathyroids in chickens is followed by tetany consisting of involuntary twitching and spasm of skeletal muscles due to an increased excitability of peripheral neuromuscular mechanisms. These signs increase in severity, convulsions follow and most birds die within two days after removal of the parathyroids (Doyon and Jouty, 1904) "Parathyroid tetany" is caused by a decrease in serum calcium. This decrease in serum calcium was studied in Carneau pigeons by Riddle, Rauch and Smith

(1945). The four parathyroid glands in these pigeons are located external and posterior to the thyroids. Complete parathyroidectomy can be performed without injury to the thyroid gland. Serum calcium dropped from an average of 10.8 mg. per 100 ml. to 5.8 mg. per 100 ml. after parathyroidectomy. It is of interest that the formation of endosteal bone was promoted by estrogen as effectively in the femurs of parathyroidectomized pigeons as in normal controls. The calcemia which follows the administration of estrogen is as marked in parathyroidectomized as in normal pigeons.

It is of interest that parathyroidectomy in pigeons decreases the ultrafiltrable plasma calcium. Estrogens induce no changes in the ultrafiltrable plasma calcium of either normal or parathyroidectomized pigeons. The rise in plasma calcium due to estrogens occurs in the non-ultrafiltrable fraction (Riddle and McDonald, 1945). These studies confirm the theory — to be mentioned later — that the signs of hypo- and hyper-calcemia in mammals appear to be associated with changes in the ultrafiltrable fraction of plasma calcium. Riddle and McDonald observed tetany of in parathyroidectomized pigeons treated with estrogen. The increase in the non-ultrafiltrable fraction of plasma calcium induced by estrogens did not prevent the appearance of signs of hypocalcemia due to the decrease in the ultrafiltrable fraction of plasma calcium following removal of the parathyroids.

CHAPTER VII

Mammals

Studies on the effects of thyroidectomy in mammals have been closely related to clinical investigations of thyroid deficiency in human beings. Extirpation of the thyroid gland in young mammals of all species is followed by structural and metabolic changes characteristic of juvenile hypothyroidism. Attempts to reproduce the signs of adult myxedema by removing the thyroid gland from adult animals have been less successful.

The recognition of the parathyroid glands as organs distinct from the thyroid was a prerequisite for research on the effects of thyroidectomy. The anatomy and embryology of the parathyroids was elucidated through the pioneer work of Kohn (1895). According to Kohn the two pairs of parathyroid glands found in most mammals develop from the dorsal diverticula of the third and fourth pharyngeal pouches and are therefore designated as parathyroids III and IV. Parathyroids IV are often found embedded in the thyroid substance and are therefore called internal parathyroids. They are missing in some species like the rat Because of this fact and the ease with which the parathyroids III (external parathyroids) can be removed without injuring the thyroid, the rat is an excellent subject for studies on the effects of total parathyroidectomy. Not only the number and position of the parathyroid glands vary among the different species of mammals, even among members of the same species, e g., the pig, variations have been reported. There is a wealth

of information on this subject in the studies on the comparative anatomy of the thyroid and parathyroid gland by Forsyth (1918). The Italian investigators, Vassale and Generali (1896) were the first to perform complete parathyroidectomies on the basis of Kohn's work. They extirpated both internal and external parathyroids in cats and dogs. The animals presented a typical syndrome. The operation was followed by fibrillary contractions and muscular spasms, rigid and uncertain gait, tachycardia, rapid emaciation, and death within a few days. Death occurred in most of the dogs on the third or fourth day, in most of the cats on the fifth day following operation.

Horsley in 1886 recognized the influence of age on the results of what he believed to be thyroidectomy in cats and dogs. It is most probable, however, that the parathyroids were removed together with the thyroids in Horsley's experiments. He states: "I find that the determining *factor, par excellence, of the value of the gland as regards* its influence on the general metabolic processes of the animal is age. The effect of removing the gland in the young animal is the rapid appearance of violent nervous symptoms and death in a few days; in an older animal, e.g., a one year old dog, the symptoms are less violent, later in their appearance and the animal survives perhaps for three weeks, in a very old animal the removal of the gland simply hastens the torpor of old age. These observations refer to cats and dogs."

Berkeley and Beebe (1909) stated that the symptoms following total parathyroidectomy without removal of the thyroid glands are more severe in young than in old dogs.

Considerable experimental evidence has accumulated to prove that in mammals the sensitivity to the administration of thyroid hormone increases with age.

Bodansky and Duff (1936) showed that rats, 22 to 36 days old at the beginning of thyroid treatment, continued to grow even when given injections of one mg. of thyroxin daily. The same dose caused rapid loss of weight and death in adult animals weighing five to 10 times as much. Young rats of from 20 to 50 g. body weight increased steadily in weight even when given a daily dose of 0.25 mg. of thyroxin. Older rats weighing about 100 g. showed a standstill or slight decrease of body weight on the same dose of thyroxin (Abderhalden and Wertheimer, 1929). Belasco and Murlin (1941) found that the increase in basal metabolic rate produced in rats by a given dose of thyroxin (2 mg. per kg. body weight) was significantly less at two months of age than at 18 months.

LeBreton and Schaeffer (1935) have made studies on the effect of thyroxin on rabbits of different age groups. A single injection of 2 mg. per kg. of body weight into rabbits weighing less than 350 g. produced no change in basal metabolic rate. In rabbits weighing from 350 to 600 g., the increase in basal metabolic rate was 15 per cent; in rabbits from 650 to 800 g., the increase was 25 per cent In adult rabbits, the same dose of 2 mg. per kg body weight produced an elevation of basal metabolic rate up to 52 per cent. Similar results were reported by Roelandts and de Waele (1936). Marine (1939) has stated as a general principle that immature animals are less sensitive to thyroxin than adults The same is true for human beings Children tolerate larger doses of thyroxin than do adults (Mautner, 1941).

These findings are in accordance with the assumption of a high level of thyroid function during growth and development. The sensitivity to exogenous thyroxin is inverse to the level of the thyroid hormone in the body. Means and Richardson (1938) in their monograph on

thyroid diseases, state that "the effect of the hormone, as would be the case with any catalyst, is greatest when its concentration at the start is lowest." It has been shown that sensitivity to thyroid medication, as measured by the response of serum cholesterol, is greater in children suffering from hypothyroidism than in euthyroid children (Wilkins and Fleischmann, 1941). In a hypothyroid child a single dose of thyroxin (2 mg.) causes a noticeable decrease in serum cholesterol. This effect lasts for a period of about forty days before the cholesterol returns to its previous high level. In a normal child the same dose of thyroxin causes only a slight and transient lowering of the level of cholesterol. The basic metabolic rate of thyroidectomized rabbits responds to thyroxin with a greater rise than the basal metabolic rate of controls. The thyroidectomized rat has been found to give a metabolic response to a daily injection of 6 micrograms of thyroxin per kg. of body weight, an amount inadequate to produce any increase in the oxygen uptake of normal animals (Barker *et al.*, 1949). Andik *et al.*, (1949) have reported that the basal metabolic rate of the thyroidectomized rat shows a significant rise following the injection of a single dose of 2 micrograms of thyroxin per kg. of body weight.

An important contribution to this problem is the finding of the MacKenzies (1943) that the degree of hyperplasia of the thyroid due to administration of sulfaguanidine decreases with age. The thyroid hyperplasia which occurs under the influence of sulfaguanidine is considered to be compensatory to the failure of the thyroid hormone. Therefore, the small increase in thyroid weight in older rats indicates a decrease of the amount of thyroid hormone required by the tissues of older animals. The blocking of thyroxin synthesis by some of the sulfonamides and by

thiourea and its derivatives should prove a valuable tool in studying the influence of age on the effects of thyroidectomy in various species. Experimental cretinism in rats has been produced through continued administration of thiouracil from the time of birth on (Dempsey and Astwood, 1943, Hughes, 1944). By incorporating thiourea in the diet of the pregnant rat, the production of thyroid hormone was inhibited even prior to birth. Following parturition, the cretin rats received the anti-thyroid drug from the mother's milk and after weaning, directly from the thiourea diet. These rats grew at a definitely retarded rate, weighing an average of 64 g. at the age of 84 days. The weight of untreated rats from untreated mothers at the same age was 160 g. (Goldsmith, 1949).

The maintenance of normal thyroid weight by the administration of thyroxin in rats simultaneously treated with thiouracil has been used to estimate the amount of thyroxin produced (Dempsey and Astwood, 1943). Daily doses of 9.5 micrograms, 5.2 micrograms and 1.7 micrograms of thyroxin are required to maintain the weight of the thyroid of young male rats kept at environmental temperature of 1°, 25°, and 35° C. respectively. These doses are considered to be equivalent to the amount of hormone produced by the normal thyroid gland at each of these ambient temperatures. It is probable that the stimulus to the thyroid to increase its hormone production is mediated through the pituitary gland Thyrotrophic hormone has been demonstrated in the urine of rats exposed to cold (Brolin, 1945). The thyroid seems to be of importance for survival in a cold environment. Rats made hypothyroid by feeding them thiouracil survived from three to seven days when exposed to an environment of 2° C. Thyroxin administered in doses as low as 2.5 micrograms per day was

effective in maintaining life in thiouracil-fed rats exposed to the same temperature for an experimental period of 28 days (Ershoff, 1948).

Rats placed on a stock diet with thiouracil added both to the food and water show a slower decline in metabolic and heart rates than thyroidectomized rats. This may be due to the presence of thyroid hormone stored in the gland. The final metabolic rates, however, were about equal in the rats "chemically thyroidectomized" with thiouracil and those in which the thyroid had been removed surgically. In both groups the basal metabolic rate was decreased by from -34 to -41 percent (Meyer and Ransom, 1945).

I^{131} in doses from 3 to 50 millicuries per kg. were given to young mice on a normal diet. Doses of 50 millicuries per kg. resulted in complete destruction of the thyroid and the parathyroid within a few days. Lower doses (3 to 5 millicuries per kg.) permitted survival of some thyroidal epithelium in the isthmus and cranial apex of the thyroid for as long as 120 days after injection, but resulted in loss of the parathyroid gland (Gorbman, 1947). Total thyroid destruction was achieved in the new-born rat by the injection of 16 millicuries of I^{131} per kg. In this case the parathyroids survived (Goldberg and Chaikoff, 1949).

Vitamin A in large doses reduces the weight of the thyroid gland and diminishes the basal metabolic rate of rats (Sadhu and Brody, 1947). The hyperplasia and hyperemia of the thyroid glands of rats treated with thiouracil can be neutralized to some extent by administering the methylether of Vitamin A simultaneously with the antithyroid drug (Studer, 1948).

Erdheim was the first to investigate the effects of parathyroidectomy on the rat (1911). He used electrocautery for destruction of the parathyroids and made serial sections of all neck organs at autopsy. In most of the animals in

which all parathyroid tissue had been destroyed, tetany appeared three to seven days after operation. If only half of one parathyroid was left intact, either no signs or very mild signs of parathyroid deficiency followed. In animals which survived the operation for one month, the incisor teeth became soft and bent, and ultimately fell out. Erdheim described the histologic picture of these lesions in the enamel of the incisor teeth, which he ascribed to a lack of calcium in the growing dental tissues.

Hammett (1927) studied the mortality rate after thyroparathyroidectomy and parathyroidectomy in the rat. He came to the conclusion that the effects of glandular deficiency are more severe in the young than in the older rat. Animals operated upon later in life have a lower mortality rate than those operated upon earlier. Young rats are also more susceptible to cataract formation, due to parathyroid deficiency, than older animals (Goldmann, 1929).

Salmon (1938) has analyzed the body growth of rats thyro-parathyroidectomized at birth. Rats are well adapted for these studies because they are very immature at birth, and the characteristic structure of the thyroid develops only during the last three days in utero (Kull, 1926). This is in good accordance with the finding that radioactive iodine is stored in the thyroid of the rat only towards the end of fetal life (Gorbman and Evans, 1946). The newborn rat has, therefore, had very little, if any, benefit of its own thyroid. Growth of the rats thyro-parathyroidectomized at birth reaches a growth plateau after three weeks. This represents the inherent growth capacity of the organism. Normal growth response was not obtained when newborn thyro-parathyroidectomized rats were given either thyroid or parathyroid hormone alone. Normal growth curves were obtained only when they were given both the thyroid and the parathyroid hormones Pituitary implants

administered to thyroparathyroidectomized rats aft weaning time did not produce a growth response if a thyroid tissue had been removed at birth. Only when thy roid remnants were present, a growth response was ob tained. This was in contrast to experiments of P. E. Smit (1933), who obtained growth in thyroidectomized rat with anterior pituitary implants. However, Smith's rat were considerably older (40 days) when their thyroid were removed. Salmon offers the explanation that the thy roid may be the predominant influence in the early stages o development during the first days after birth. Later th pituitary may become independent of the thyroid and pre dominant in the expression of the developmental patter inherent in the tissues of the body. Another factor con sidered by Salmon is the response capacity of the tissues It may well be that the body tissues as the end organs o hormonal actions need to be primed with thyroid before they can respond to pituitary growth hormones. The rats thyroidectomized by Smith at the age of 40 days had the benefit of their thyroid gland until shortly before the im-plantation of pituitary tissue. Compared with these older animals, Salmon's new-born rats had been exposed only for a short time to thyroid hormone. The importance of the thyroid hormone for the early growth and develop-ment of the rat has been shown again recently (Scow *et al.*, 1949). Rats were thyro-parathyroidectomized at birth. They received injections of pituitary growth hormone or thyroxin or both hormones from 31 to 61 days of age. The rats receiving thyroxin alone or in combination with the growth hormone tripled their body weight during this period of 30 days. Their body form, ears, fur and genitalia showed marked development. Their osseous development advanced to a stage comparable to that of a 40 day old normal rat. The rats receiving growth hormone alone

doubled their weight. However, their body form, ears, fur and genitalia remained immature as in the thyro-parathyroidectomized controls untreated by hormones. The osseous development of the controls and of the operated rats treated with growth hormone alone advanced only three days.

Subcutaneous injections of thyroxin in normal female rats over a period of 251 days caused no perceptible increase grossly or histologically in the rate of endochondral ossification in the tibia or the rib. Rats on whom thyroparathyroidectomy had been performed at the age of about 40 days showed marked dwarfism after a post-operative period of 330 days Histologically, the picture of endochondral ossification resembled that following hypophysectomy, although the changes were not as severe. Decrease in the size of chondrocytes, deposition of bone along the zone of erosion, very light formation of cancellous bone, and marked increase in the fat content of the marrow were noticed. Injections of thyroxin were followed by a return to normal in gross and histologic appearance. Injection of thyroxin in the rats from which not only the thyroid and parathyroid, but also the pituitary gland had been removed, had no effect in repairing the growth deficiency (Becks, Ray, Simpson, and Evans, 1942). Feeding of thyroid does not produce a specific catabolic effect upon the calcium deposits in the bones of normal rats, if the calcium intake is adequate (Smith and McLean, 1938).

Hypothyroidism induced by thiouracil has no effect upon the reproductive system of the adult male rat, as judged by the ability to sire litters Prolonged thiouracil administration, associated with hypothyroidism in the adult female rat does not cause sterility but does interfere with continuation of gestation, causing the resorption of embryos (Jones, Delfs and Foote, 1946).

An excess or lack of parathyroid hormone does not affect reproduction. Parathyroid hormone was given to female rats by protracted administration in doses sufficient to induce hypercalcemia and osteoclasis. The reproductive organs showed no significant changes and the estrus cycle remained undisturbed (Neuweiler, 1933). Similarly, removal of the parathyroids did not interfere with the estrus cycle or with reproduction in the rat (Chandler, 1932).

Recent work on rats using radioactive phosphorus has proved that the primary effect of the parathyroid extract is to inhibit the reabsorption of phosphate by the renal tubules. The prompt action of five units of parathyroid extract in promoting the urinary excretion of administered P^{32} in the parathyroidectomized rat is evidence of the direct action of the parathyroid hormone on the kidney (Tweedy *et al.*, 1947). This work corroborates Albright's concept of the mechanism of action of parathyroid hormone. "The parathyroid hormone exerts its primary effect on the kidney and thereby increases the phosphorus excretion in the urine. This lowers the level of inorganic phosphorus in the serum, which in turn is restored to normal by an increased resorption of phosphorus and calcium from the bones, so that the serum calcium level rises. When the serum calcium becomes sufficiently elevated, increased amounts of calcium are excreted with the urine" (Albright, 1941).

Changes in renal excretion of phosphate due to exogenous parathyroid hormone can be demonstrated in parathyroidectomized, but not in normal rats (Stoerck and Silber, 1949). This shows that the level of circulating parathyroid hormone determines the sensitivity to parathyroid hormone in the same way as the level of circulating thyroid hormone determines the sensitivity to thyroid hormone (*page 29*).

However, as Howard (1951) has recently pointed out in an excellent review on calcium and phosphorus metabolism, the parathyroid hormone does not act solely by inducing increased excretion of phosphorus and a fall in serum phosphorus. It has been demonstrated that parathyroid hormone has a direct decalcifying effect on bones even in nephrectomized rats. This effect is independent of the acidosis produced by nephrectomy.

The relationship between dietary calcium and serum calcium in relation to the level of parathyroid hormone has been clarified by Bulbring (1931). The effects of high calcium, low calcium and normal diets on serum calcium are shown in Table II (after Bulbring).

A fundamental difference seems to exist between the regulatory mechanism governing the function of the thyroid and parathyroid glands. Regulation of the function of the thyroid by the pituitary is a well established fact. Evidence for regulation of the parathyroid by the pituitary is lacking. In fact, all experimental evidence indicates that the parathyroids are not affected by pituitary hormones. In male rats the pituitary body increases in size after removal of the thyroid gland. Removal of the parathyroids does not affect the size of the pituitary body (Brolin, 1948). The function of the parathyroid gland seems to be unimpaired in the mature male rat deprived of its pituitary gland. The hypophysectomized rat maintains its serum calcium and inorganic phosphorus levels even when subjected to the stress of a low calcium diet. Rats deprived both of their pituitary and their parathyroid glands suffer a profound fall in serum calcium and rise in serum phosphate (Carnes *et al.*, 1943). The independence of the parathyroid from the pituitary has been shown recently by a histochemical method. The enzyme, alkaline phosphatase, disappears from the thyroid after hypophy-

sectomy of the rat. On the other hand, alkaline phosphatase persists in the parathyroid after hypophysectomy (Dempsey *et al.*, 1949).

TABLE II

INFLUENCE OF DIETARY CALCIUM ON SERUM CALCIUM IN RATS

Serum calcium (mg. per 100 ml.)

Calcium content of diet in per cent	Controls	Parathyroid-ectomized	Treated with parathyroid hormone
86	10 66±0 21*	9.23±0.18	12.58±0.25
.46	10 66±0 20	6 28±0.13	10 55±0.21
.03	10 37±0 21	6 35±0 13	9 75±0 19

* Standard Error of the Mean

In young rabbits thyroidectomy produces very similar changes in growth and development to those observed in man. The thyroid was removed from rabbits at the age of three weeks. Two weeks after operation the hair had become dry and did not lie flat and smooth on the skin. Ten weeks after operation the average weight of the operated rabbits was 750 gm. The unoperated controls had attained a weight of 1400 gm. at the same age. The hair of the thyroidectomized animals became coarse and the skin dry, thick and scaly. The abdomen grew out of proportion to the rest of the body, and gradually a "pot belly" developed. The animals were sluggish and moved about very reluctantly. No myxedematous changes of the skin were noticed (Basinger, 1916). Basinger's work confirmed and amplified earlier work of Hofmeister (1894), who, in addition to the signs of hypothyroidism, had reported hypertrophy of the pituitary gland. Furthermore, he noticed disturbances in the growth of the cartilages of the epiphyses of the long bones, consisting mainly of a decreased rate of cellular growth activity and a swelling vacuolization of the cartilage. Hofmeister used the term chondrodystrophia

thyropriva for this disturbance in the growth of the cartilages in young thyroidectomized rabbits Wilkins (1941) has described a disturbance in the cartilage just prior to ossification in hypothyroid children. This disturbance is presumably the cause of epiphyseal dysgenesis associated with hypothyroidism, a condition manifested by the appearance in the cartilages of multiple irregular islets of ossification scattered over a large area. These enlarge and coalesce to form an irregular, spongy porous or fluffy mass. Hunter and Sawin (1942) have made a careful study of the effects of thyroidectomy on the skull of the domestic rabbit. An analysis of skull contour in thyroidectomized rabbits indicates the presence of different degrees of retardation in proportion to the rate of growth, both in bones preformed in cartilage and in membranes. The anomalies of the skull, teeth and jaws arising under this condition are due to a general lowering of physiologic activity which includes a restriction in the internal resorption of bone, but which does not include the continuously growing teeth. Developmental anomalies arise as a consequence of the slow growth of skull and jaws and the normal growth of teeth.

The rabbit is the only mammal in which changes of pigmentation due to exogenous thyroid hormones have been reported Iljin (1932) found that desiccated thyroid fed in large doses (0.56 g. daily) produced growth of white hair instead of black on the ears of the black Russian rabbit.

The metabolic changes in the adult rabbit resemble closely those observed in human beings As mentioned before, total thyroidectomy in this species can be performed without risk of hypoparathyroidism. On the fifth to seventh day after thyroidectomy, the basal metabolic rate begins to fall and reaches its lowest level of about 35

per cent below the preoperative level between the 20th and 30th day (Marine and Lenhart, 1920). Changes in serum cholesterol due to thyroidectomy resemble the changes in hypothyroid human beings after withdrawal of thyroid treatment. Thyroidectomy in the rabbit is followed by a sharp rise of the serum cholesterol level from the preoperative level of from 60 to 100 mg. per 100 ml. to levels of from 140 to 280 mg. per 100 ml. After the first rise, the serum cholesterol fluctuates markedly, finally becoming stabilized after about 12 weeks at a value of about 180 mg. per 100 ml. (Fleischmann, Shumacker and Wilkins, 1940).

The following experiments on the relationship of serum cholesterol to total body cholesterol suggest that the thyroid hormone influences the shift of cholesterol from the blood plasma into the tissues, rather than the destruction of cholesterol in the body. The results of thyroidectomy in four rabbits of about five weeks of age are shown in Table III. In all of them, hypercholesterolemia developed rapidly after operation. Three of these animals (Nos. 3, 4, 5) were sacrificed at the same time as two normal rabbits of about the same age (Nos. 1, 2). The intestines were removed and the total body cholesterol determined. Although the serum cholesterol level had been more than doubled in the operated animals, the concentration of cholesterol in the body was practically unchanged. The fourth animal of the operated group (No. 6) whose serum cholesterol one week after operation was 190 mg. per 100 ml. was treated for a week with thyroxin. The total amount administered was 0.4 mg. The rabbit showed loss of weight and other signs of hyperthyroidism. It was sacrificed and found to have the highest percentage of total body cholesterol (.242) and the lowest serum cholesterol, 58 mg. per 100 ml. of all the rabbits analyzed (Fleischmann and Shumacker, 1942).

The rabbit, in spite of the frequent occurrence of acces-

TABLE III

EFFECT OF THYROIDECTOMY ON TOTAL BODY AND SERUM CHOLESTEROL OF RABBITS

No.	Weight	Total Body Cholesterol	Cholesterol Per Cent of Body Weight	Serum Cholesterol	
	gm	mg.		mg per 100 ml.	
1	463	780	.168	88	Normal
2	360	525	.146	98	Normal
3	450	735	163	203	Thyroidectomized
4	475	780	.164	230	Thyroidectomized
5	653	915	140	236	Thyroidectomized
6	248	600	242	58	Thyroidectomized, then treated with thyroxin

sory parathyroids, succumbs to removal of the parathyroid glands with a violent and intractable tetany, in which the increase in serum inorganic phosphate is often more striking than the decrease in serum calcium (Thomson and Collip, 1932).

In the guinea pig prolonged treatment with gradually increasing doses of parathyroid hormone leads to the severe resorption and decalcification of the bone characteristic of osteitis fibrosa in human beings. Bones taken from young guinea pigs 18 hours after injection of parathyroid hormone already show extensive resorption of the cortical and spongy bone as a result of the removal of calicum from the bones (Bodansky, Blair and Jaffe, 1930).

The effects of thyroidectomy on the reproductive organs in males of the annual-breeding ground squirrel, *Citellus tridecemlineatus*, have been studied by Zalesky and Wells (1937). Thyroidectomy was performed during the period of sexual quiescence. The squirrels were sacrificed during the period in which the reproductive organs are

normally well developed. The experimental animals did not show the same degree of sexual development attained by the controls during the breeding period. The testes were reduced to an essentially infantile condition and there was no evidence of spermatogenesis.

In the Syrian hamster, *Cricetus auratus*, addition of thiouracil to the diet in a concentration of 0.1 per cent produces hypertrophy of the thyroid epithelium and diminution of colloid within four weeks (Harris *et al.*, 1946).

During hibernation the thyroid of such animals as the hedgehog (*Erinaceus europaeus*) undergoes atrophic changes. These are characterized by considerable flattening of the epithelium and a diminution of colloid. Decreased thyroid activity was thought to be a causative factor in the onset of hibernation. However, hibernation and awakening from hibernation occurs in thyroidectomized hedgehogs. This proves that hibernation cannot be caused primarily by changes in thyroid function (Uiberall, 1934). The changes in the thyroid gland are most likely unspecific signs of decreased activity found also in other organs during hibernation.

Dogs are very insensitive to thyroid deficiency. Only in dogs thyroidectomized prior to the age of 28 days was marked lack of growth and osification observed and this was transient (Binswanger, 1936). If thyroidectomy was performed at an age of more than 28 days the rate of growth was not impaired. Binswanger did very careful autopsies of his experimental animals to make sure that parathyroid tissue was present and to rule out the presence of accessory thyroid tissue. He weighed the thyroid glands and found that the [illegible] oid gland is 0.18 per cent of the bo[illegible] weeks of life, and only 0.02 per [illegible]

The marked differences

of a dog and man have been elucidated by the studies of Danowski *et al.* (1946), and of Glock (1949). The level of circulating hormone, as measured by the concentration of precipitable iodine in the serum is always much lower in dogs than it is in human subjects, and the concentration may normally be too low to detect. The concentrations range from zero to 2.4 micrograms per 100 ml. in the dog as compared to a range from 3.0 to 8.0 micrograms per 100 ml. observed in normal human subjects. The dog, in proportion to his body weight, has a much greater capacity than does man to inactivate or destroy exogenous thyroid hormone. With desiccated thyroid in daily doses of 0.77 gm. an increased consumption of oxygen and a loss of body weight was observed despite a well-maintained intake of food. With continued ingestion of thyroid this initial response was followed by a return of protein-bound serum iodine, oxygen consumption and body weight towards pretreatment level (Danowski *et al.*, 1946). Only with doses of 30 gm. of desiccated thyroid given daily by mouth, dogs lose weight rapidly and die in less than two months (Hesse *et al.*, 1933).

The "chemically thyroidectomized" dog is nearly as insensitive to exogenous thyroid as the normal dog (Danowski *et al.*, 1946). The author found that surgically thyrodectomized adult dogs could tolerate daily doses of 64 mg./kg. for many weeks without any symptoms of hyperthyroidism (Fleischmann *et al.*, 1949).

Glock (1949) has studied the effects of feeding 0.1 per cent thiouracil in the diet to a litter of eight weeks old puppies and to adult dogs None of the dogs showed any outward manifestations of hypothyroidism. The rate of growth of the puppies was unaffected and the weights of the adult dogs were maintained at a fairly constant level. The thyroids were considerably enlarged and showed

marked hyperplasia. The total serum cholesterol values rose to a maximum (up to 600 mg. per 100 ml.) after several months on the diet and then fell to values of from 250 to 300 mg. per 100 ml. These levels were considerably higher than the cholesterol levels of the control dogs, which ranged from 80 to 150 mg. per 100 ml.

Mayer (1947) made similar observations on beagle puppies treated with large doses of propylthiouracil from their fifth or sixth week of age. No difference was noted between the experimental dogs and the controls with regard to rate of growth, appearance and behavior and ossification of tibial epiphyses and ribs. The thyroid gland showed the typical effects of poisoning with an antithyroid compound. Mayer's paper is of great interest because he worked on a pure breed of dogs instead of on mongrels as most authors.

Difficulties in forming conditioned reflexes in thryoidectomized dogs were observed by Asimoff (1928). The ability to form and differentiate conditioned reflexes is impaired similarly in hypothyroid children (Gantt and Fleischmann, 1948).

Most dogs are restless one day after removal of the parathyroid glands. Fibrillary tremors of the muscles become more and more distinct and the dog may pass rapidly into a condition in which all the muscles are in rigid spasm, but as a rule the tremors are accompanied by chorea-like movements of the whole limbs or segments of the limb The dog is able to walk at first, but with a stiff and awkward gait, however, he may suddenly fall to the floor in an epileptic form of convulsion; the legs are stretched out rigid, the head stretched forward, all the muscles of the neck being thrown into tetanic contraction, breathing stops for a few moments and is then gradually resumed, the

legs finally relax and the dog recovers and walks about again. It was the main contribution of MacCallum to recognize that this condition is due to calcium deficiency and can be relieved promptly by intravenous injection of calcium chloride or calcium gluconate. MacCallum and Voegtlin (1909) found the average serum calcium level to be 13.3 mg. per 100 ml. in normal dogs, 5.7 mg. per 100 ml. in parathyroidectomized dogs. The tetany of parathyroidectomized dogs could also be prevented by injection of an extract of the parathyroid glands of the ox (Collip, 1925). The rise in serum calcium produced by a standard dose of this extract is more marked in the parathyroidectomized than in the normal dog (Collip, Clark and Scott, 1925).

Pregnancy accelerates and intensifies the tetanic disturbances following parathyroidectomy of the bitch (Carlson, 1913). In human beings the bone disease, osteitis fibrosa, is a result of hyperactivity of the parathyroid glands. In puppies, Bodansky and Jaffe (1931) produced the characteristic generalized lesions of osteitis fibrosa by the injection of parathyroid hormone. Injections were started when the puppies were from six to nine weeks old with 2 units per kg. daily. The injections were continued for about three months staggering the dose to 6 units per kg. The normal bone development is dependent on a normal level of calcium and inorganic serum phosphorus in the serum. It is of little importance by which means this level is obtained Kozelka, Hart and Bohrstedt (1933) found that normal bone development can occur in parathyroidectomized dogs by giving sufficient vitamin D to obtain normal serum calcium and inorganic phosphorus levels Chronic poisoning with large doses of parathyroid hormone leads to calcium deposits in the lungs, the stomach

and the kidneys. The aortae of these dogs were relatively free from calcium deposits (Hueper, 1927; von Brand *et al.*, 1932).

Following injections of parathyroid extract in the young dog, a considerable decrease in the rate of reabsorption of phosphate by the renal tubules and a consequent reduction in the concentration of phosphate in the plasma was observed (Harrison and Harrison, 1941).

The sequence of signs after removal of the parathyroids is the same in the cat as in the dog. Absence of severe tetany in parathyroidectomized cats could be correlated with the presence of accessory parathyroids. Pregnancy has no effect on the development of tetany in the cat (Carlson, 1913).

McLean *et al.* (1935) have made careful studies of the state of calcium in the serum of the cat. Of the total serum calcium about half is combined with protein, the ultrafiltrable remainder is largely in the ionized form. The signs of hypo- and hypercalcemia appear to be associated with changes in the level of the ionized fraction (Ca^{++}). The normal range of Ca^{++} was found to be between 4.2 and 5.0 mg. per 100 ml. Acute tetany after thyro-parathyroidectomy developed only when the Ca^{++} in the serum was found to be 2.6 mg. per 100 ml. or less.

Complete thyro-parathyroidectomy had no effect on the adult fox; autopsies showed that no discoverable remnants or accessory glands had been left behind (Carlson and Woelfel, 1910).

The influence of the age factor on the effects of thyroidectomy is very marked in ruminants. In young goats and sheep, von Eiselsberg (1895) observed signs strongly resembling cretinism in man. Von Eiselsberg describes sheep operated upon at the age of 10 days with a marked retardation of growth and mental sluggishness. At autopsy

retardation of osseous development and atherosclerosis of the aorta were the most significant findings. In goats operated upon at the age of three weeks, retardation of growth could be observed one month after operation. Four months after operation the control animal weighed double the amount of the thyroidectomized kid. The growth of the extremities was more retarded than that of the trunk. The abdomen had the appearance of being inflated Sexual development was retarded, as was growth of the horns, both in sheep and goats. The striking difference in the effects of thyroidectomy in sheep and goats is in the effect on hair growth. In operated lambs, the hair was scanty and short. In the thyroidectomized kids, however, the hair grew much longer than in the controls but could be pulled out easily by hand. The only physiological observation on the thyroidectomized kids was a lowering of the body temperature. Pick and Pineles (1909) observed myxedematous swelling of the skin in goats thyrodectomized at the age of six and eight weeks.

A careful investigation of the effects of removal of the thyroid and parathyroid glands on sheep and goats was made by Simpson (1913). He removed the thyroid glands together with the internal and external parathyroid glands, from four lambs and four adult sheep. The lambs all showed acute signs of tetany shortly after the operation and died. In the adult sheep such results were not noted during the time they were under observation — three to four months. In the adult sheep complete removal of the thyroid and parathyroid glands produced no signs resembling myxedema or tetany in the human subject. No lowering of the body temperature and no tendency for the wool to fall off were noted. There was no evidence of mental impairment, the operated animals stayed alert and brisk in their movements. They gave birth to full-term

healthy lambs, which they suckled. Simpson published further experiments on this subject in 1924 (a, b). In 16 pairs of twin lambs, the thyroid gland was removed from one animal of each pair, and the other was kept as a control. The external parathyroid was conserved in these experiments. When the operation was performed from three to four weeks after birth, marked stunting resulted. In more than one instance, the weight of the control was three times that of the thyroidectomized animal. When thyroidectomy was delayed until the third or fourth month the retardation of growth was only slight. If thyroidectomy with conservation of the external parathyroids was performed on young adult sheep or on lambs at the age of six to seven months, for about a half year subsequent to the operation nothing in the general appearance of the animal would suggest that the thyroid gland had been removed; if kept alive for a year or longer, chronic changes, ovine myxedema, would appear. The hind limbs became swollen, the movements became slow and clumsy, the musculature flabby, the gait quite unlike that of normal sheep. The rapidity with which symptoms develop seems to depend on the age at which the operation is performed. Simpson reiterated his earlier statement, that in old adult sheep the thyroid gland may hardly be missed. Some degree of slowing of the pulse may be the only sign of thyroid deficiency.

Marston and Pierce (1932) studied the effects of thyroidectomy in adult merino sheep. Mature merino sheep, operated upon at the age of 12 months, suffered little obvious change in their appearance. The amount of wool fleece grown was decreased. The basal metabolic rate became markedly retarded, and dropped to − 40 per cent in some cases. Young merino sheep showed stunted growth and considerable changes in appearance, resembling hu-

man cretins. The wool was reduced considerably without evident decrease in fibre diameter, and the degree or greasiness of the fleece was definitely lessened. No symptoms of edematous infiltration of the integument were observed in any of the operated animals. The external parathyroids were left intact in these experiments.

The skulls and skeletons of the sheep on which Simpson made his studies on growth were studied in detail by Todd *et al*, (1938). The authors based their report on the study of the bones of five pairs of twin sheep, one of each pair being thyroidectomized in early life. The general results of thyroidectomy are deficient growth and modelling of the epiphyses themselves, defective development of age characteristics on both epiphyses and adjacent shaft, and diminished velocity of the growth of the shaft. There is no modification of bone texture, weight, thickness or modelling of the shaft, and no prolongation of the growth period to compensate for diminished velocity of growth. The point of damage to both growth and maturation patterns is definitely the diaphysio-epiphysial plane. The direct effect of hypothyroidism is probably restricted purely to the modification of growth velocity. The effect on maturation seems to be indirect, produced through disturbance of the bodily endocrine pattern.

The effect upon the growth pattern of the skeleton is to produce what seems to be a progressively more marked inhibition but is really an inhibition of velocity without prolongation of the growth period. The result is to reduce the proportions of the limbs of the domesticated sheep to those of the wild sheep. The effect on maturation is to reduce velocity approximately by one-half. Probably like the growth impulse, maturation progress in the skeleton ultimately fades out. Obvious pathological changes in the diaphysio-epiphysial plane are not evident until the

animal is two years old or more. The pathological features are irregular exuberances on the shaft end, and inturned epiphysial margins, and a small poorly modelled, ill-fitting *epiphysis scarcely covering the shaft end.*

It is of interest that the formation of a simple tactile conditioned reflex in adult sheep is not affected by thyroidectomy (Lidell and Simpson, 1926).

Simpson (1924b) removed the thyroids from two of triplet female goat kids at the age of 20 days. A difference in growth rate was detectable on the nineteenth day following operation, and from that time on the normal kid rapidly outgrew the thyroidectomized kids. Moussu (1892) produced the signs of juvenile hypothyroidism in a goat operated upon at the age of 10 days; at the age of six months this animal looked like an animal one month old. Complete absence of cutaneous swelling (myxedema) was noticed.

It has been known for some time that thyroidectomy of the lactating goat causes a reduction in milk production (Grimmer, 1918). An interesting change in the composition of goat's milk following thyroidectomy was observed by Fasold and Heidemann (1933). Normal goat's milk contains vitamin A but no carotene; even if the diet is rich in carotene, none is excreted with the milk under normal conditions. The milk of thyroidectomized goats contains enough carotene to change its color to yellow; vitamin A, however, is absent from the milk after thyroidectomy. Investigations of the Missouri Agricultural Station (Ralston *et al.*, 1940) showed that four weeks after thyroidectomy of the lactating goat, milk production had decreased 70.8 per cent. The heart rate decreased from 86 to 80 beats, which is hardly significant. In these experiments the parathyroids were conserved. Complete removal of the thyroids and parathyroids in goats ranging

in age from two to 16 months does not result in tetany. Tetany does not supervene because the goat can maintain a normal or nearly normal level of blood calcium in the absence of its parathyroids. The average level of serum calcium before operation was 9.7 mg. per 100 ml., after operation 8.7 mg. per 100 ml. No parathyroid tissue was found at autopsy. The goats operated at two months showed evidence of hypothyroidism; no evidence of thyroid deficiency was found in goats operated at a later stage (Larson and Elkourie, 1928).

Goats have also been used for a study of the excretion of exogenous thyroxin. Thyroxin was injected subcutaneously into goats and the feces and urine were examined for biologically active material. The biological activity was assayed by its effect on the thyroid weights of baby chicks treated with thiouracil. It was found that the feces contained active material during the last five days of a 10 day injection period. No activity could be detected in the urine. Bio-assay of the urine and feces of the control animals gave negative results (Monroe and Turner, 1948).

The influence of age on the effect of thyroidectomy is very marked in the pig. Moussu (1892) produced the complete picture of juvenile hypothyroidism, including swelling of the skin, in young pigs operated at the age of one month. In adult pigs, however, thyroidectomy had no marked effect. According to Caylor and Schlotthauer (1929), the signs of hypothyroidism produced in young pigs (aged two months) are largely influenced by the diet. On a diet low in protein, high in carbohydrate, the controls gained 15.3 kg. in two months, the operated animals only 1.8 kg. The operated animals did not develop cutaneous swellings (myxedema) and remained mentally alert. On a diet high in protein, low in carbohydrates, the young pigs developed the edema of myxedema and became stupid,

inert, and lost their natural curiosity. Caylor and Schlotthauer make the interesting suggestion that the mental sluggishness may be due to the pressure of edema on the central nervous system.

Duerst (1941) has thyroidectomized adult pigs for many years and found that this enhances fat deposition. He has advocated thyroidectomy in pigs as a means of producing a greater amount of lard. From this angle thyroidectomy offers greater economical advantages than castration. Similar results have been recently reported by Mahrer and Hogan (1946), who fed rations containing 0.2 per cent thiouracil to growing swine.

Sudden death from heart failure is quite common in pigs. Tachycardia is frequently observed in these pigs for weeks prior to death At autopsy the thyroid gland frequently shows signs of extreme hyperactivity similar to those found in toxic goiter in man (Dobberstein, 1944).

The effects of iodine deficiency in pregnant sows on the offspring were studied by G. E. Smith in 1917. In some sections of Montana, hairless and otherwise defective pigs were born of apparently normal sows. They were strikingly weak and low in vitality. The most marked thing in the appearance of a typical specimen was the absence of hair. The skin was smooth, shiny and bald. Only a few tactile hairs were present on the nose. The skin, particularly around the shoulders, was thick and felt pulpy. It was semi-transparent and seemed edematous, but no fluid escaped on incision. The hoofs were thin-walled, short, brittle, and plainly in an undeveloped condition. The heart in every case examined had a persistent foramen ovale. The thyroid was dark red and presented a most constant enlargement. Microscopically a uniform hyperplasia and distension of the blood vessels was manifest. Chemical analysis showed that the average iodine content of the thyroids

of 36 affected pigs was 0.001 per cent, as against an iodine content of 0.095 per cent in the thyroids of 44 normal newborn pigs. Administration of iodine during the gestation time prevented the occurrence of this condition in the afflicted area. The author's conclusion that iodine deficiency caused a lack of function and hyperplasia of the fetal thyroid is convincing. The term "fetal athyrosis" used by Smith for this condition is, however, hardly well chosen.

In goiter areas in the Austrian Alps a similar syndrome has been described recently. According to Baumann (1948) this syndrome is known as "Dickhals" ("thick neck"). Cretinism in swine is a more appropriate term. Failure of endochondral ossification is similar to that in human cretins. The thyroid is described as hyperplastic. The colloid-free follicles are filled with high epithelium. A therapeutic test with thyroid feeding was successful and resulted in complete normalcy.

Hyperplasia of the parathyroid glands was observed in pigs fed on a diet high in phosphorus and low in calcium (Liegois and Derivaux, 1944).

Brody and Frankenbach (1942) compared the relative growth and development, metabolism, general appearance, and behavior of a Jersey heifer, thyroidectomized at the age of 45 days, with a normal control. At the age of 40 months the thyroidectomized animal was about half normal weight, its metabolism per unit surface area about 40 per cent below normal; it was completely undeveloped sexually. Feeding iodized milk protein following this age stimulated growth. Her metabolic rate was increased, her hair coat was no longer rough and coarse. There was considerable development of mammary gland and horn. Before feeding the iodized milk protein, she had never been in heat, but has exhibited heat twice since then.

A male calf was thyroidectomized at the age of four

months. For approximately 60 days following thyroidectomy the animal behaved normally. After that time, however, signs of juvenile hypothyroidism developed. The skin became thick and puffy; the hair became dry, brittle and sparse, and body fat increased. The animal was quite apathetic; lack of interest in females and of normal sexual behavior was striking. Examination of the sperm revealed normal spermatogenesis. An increase of total fat and of cholesterol in the blood was noted. Administration of thyroid hormone was followed by the appearance of normal sexual behavior (Petersen *et al.*, 1941).

In the fetus of the calf, which has a gestation time of about 285 days, thyroxin-like iodine can be detected in the thyroid gland on the sixtieth day of intrauterine life. This is prior to the appearance of histologically detectable follicle formation, which takes place at 75 to 88 days. Since other tissues of calf fetuses aged 62 to 70 days contain practically no iodine, the presence of these organic iodine compounds in the thyroid can be considered a manifestation of iodine storage by the gland at an early stage of its development. From the 75th to 118th day, the predominant histological features of the thyroid were the appearance of colloid and differentiation of the parenchyma; this was not associated with a marked increase in the iodine content of the gland (Koneff *et al.*, 1949).

In cows producing great amounts of milk (high milking cows) the level of blood calcium may decline to very low levels. This decline is associated with hyperthermia, "milk fever." The calcium balance in this condition is negative. The calcium output into the milk greatly exceeds the intake from feed. Compensatory hypertrophy of the parathyroid glands has been observed in this condition (Brody, 1945).

Retardation of dental development was observed in

colts thyroidectomized at the age of two months (Houssay and Hug, 1920).

Grafflin (1942) examined the parathyroids of the Virginia deer (*Ordocoileus virginianus corealis*) throughout the year and did not detect any changes in these glands corresponding with the shedding of antlers.

A review of the older literature reveals conflicting reports concerning the effect of thyroidectomy on monkeys. Horsley (1886) was the first to report extirpation of the thyroid in monkeys. Besides symptoms of tetany, which would be referred today to lesions of the parathyroid, he observed gradual development of "the symptoms of the disease termed myxedema by Dr. Ord and ordinary cretinism" Most of Horsley's experiments seem to have been on young monkeys (species not given), but he stated that "an older animal, if kept under ordinary circumstances, will survive for six to seven weeks, dying at the end of that time of myxedema." Horsley found that tetany occurred much more frequently in young animals than in older monkeys. Von Eiselsberg (1895) performed a total thyroidectomy which obviously involved the parathyroids in a young Barbary ape (*Macaca sylvanus*). This operation was followed by acute onset of tetany and the gradual development of sluggishness and apathy.

Other investigators failed to find any changes after removal of the thyroid gland in monkeys. In the older reports (Munk, 1897, Kishi, 1904), the species used was not stated Vincent and Jolly (1904, 1906) used both *Macaca* and *Cercopithecus;* Halpenny and Gunn (1911), *Macaca mulatta.* Kishi stated that soon after operation convulsions occurred which sometimes killed the animals. The surviving animals never exhibited symptoms of myxedema or mental apathy nor any swelling of the skin. Munk made very carful autopsies and found no traces of thyroid

tissue or only minute amounts in seventeen animals operated on. Carlson and Woelfel (1910) found that a rhesus monkey in which a (presumably total) thyroidectomy had been performed showed no evidence of even "incipient myxedema."

Fleischmann, Shumacker, and Straus (1943) studied the effects of total removal of the thyroid gland in rhesus monkeys by methods used in clinical endocrinology. Total thyroidectomy had no effect on the appearance, activity, basal metabolic rate, or serum cholesterol level of adult rhesus monkeys. In man, even incomplete thyroidectomy is nearly invariably followed by hypercholesterolemia. The rise of serum cholesterol occurs not only when toxic goiters are removed, but when the normal thyroid gland is removed in the treatment of chronic heart disease. In six adult rhesus monkeys no such change was observed following thyroidectomy. The mean of repeated serum cholesterol determinations was 123.9 ± 2.0 mg. per 100 ml. of serum before operation, and 123.5 ± 2.0 mg. after operation. The completeness of the removal of the thyroid was demonstrated both by anatomical search and by physiologic tests with thyrotrophin. The monkeys were injected with thyrotrophic hormone of the pituitary to determine whether any thyroid tissue capable of responding to this factor was present. This method is useful in gathering information on the presence or absence of functional thyroid tissue in dwarfed children (Wilkins and Fleischmann, 1941). In this work, we had found an increase in creatine excretion to be the most sensitive indicator of a response to endogenous or exogenous thyroid hormone. Thyrotrophic hormone produced a great increase in creatine excretion in the rhesus monkeys only when tested before thyroidectomy. Administration of thyroxin, however, was followed by an increased creatine output both before and

after operation. This indicates that following thyroidectomy there was either no thyroid left or only an amount insufficient to cause measurable effect after stimulation with thyrotrophic hormone. In addition to the adult rhesus monkeys, two young rhesus monkeys were thyroidectomized at the age of about eight months. Both animals showed a sharp rise of the cholesterol content of the serum following thyroidectomy. The level of serum cholesterol in one young monkey which survived the operation for 147 days reached a peak of 326 mg. per 100 ml. five weeks after operation. Complete cessation of growth was observed in this animal. These data suggest the importance of the age factor in determining the effect of thyroidectomy in the rhesus monkey.

The lack of marked effects of thyroidectomy on adult rhesus monkeys has been confirmed by Jailer, Sperry, Engle, and Smelser (1944). They worked on nine female rhesus monkeys, two of whom had their ovaries removed about one year before thyroidectomy. These two only showed a gain in weight following thyroidectomy.

Recently Aranow, Engle, and Sperry (1946) administered thiouracil to four adult female rhesus monkeys in increasing doses up to 0.8 g. daily for 14 months. No significant changes in body weight or circulation time were observed during treatment None of the monkeys showed any striking changes in degree of belligerence or of spontaneous activity. Menstrual irregularity was frequently observed during treatment The serum cholesterol did not exhibit a significant trend during treatment, but the fluctuations of the cholesterol content of the serum were greater in thiouracil treated rhesus monkeys than in untreated controls. Hyperplasia of the thyroid gland of the rhesus monkey did not occur after treatment with 0 1 g and 0 2 g of thiouracil daily for 12 weks The thyroid

gland of rhesus monkeys treated with 0.8 g. of thiouracil daily for 10 weeks showed severe hyperplasia (Engle and Aranow, 1946).

The rhesus monkey appears to be considerably less sensitive to antithyroid agents than man. Estimation of the antithyroid potencies of various compounds was made on the basis of radioiodine collection by the thyroid after injection of carrier free radioiodine (I^{131}). The degree and duration of alteration of an established rate of accumulation by the thyroid gland was taken as a yardstick of sensitivity to antithyroid compounds. Comparison with data on man indicates that five to 10 times as much antithyroid drug is required to produce comparable thyroid inhibition in the rhesus monkey than in man (McGinty and Wilson, 1949).

Removal of the parathyroids without injury to the thyroid leads to the typical picture of tetany in the rhesus monkey. The sequence of events — muscular tremors increasing in frequency, convulsions and death — is similar to that observed in dogs (Biedl, 1916). The rhesus monkey is less sensitive than the dog to exogenous parathyroid hormone. A comparison of the dose of parathyroid hormone necessary to raise the level of calcium in the serum by 5 mg. per 100 ml. reveals great species differences in sensitivity. The dose is 5 i.u. (international units) for the dog, 14 i.u. for the cat; 35 i.u. for the rhesus monkey, 100 to 200 i.u. for the rabbit; and 1300 i.u. for the guinea pig (von Brand *et al*, 1932).

In human beings removal of the greater part of the normal thyroid gland in the treatment of chronic heart disease induces the signs of hypothyroidism. Gilligan, Volk, Davis and Blumgart (1934) have made careful studies of the rise in cholesterol and the drop in basal metabolic rate after this operation. Their series include patients

over 60 years of age who showed not only changes in metabolism but also untoward clinical symptoms of myxedema. Raab (1945) has treated eight patients over 60 years of age with thiouracil for relief of angina pectoris. In seven of these there was a marked response to the antithyroid drug, as evidenced by a drop in basal metabolic rate. Serum cholesterol showed a marked rise in one case, a woman of 67. It rose to a level of 619 mg per 100 ml. Wilson and Mayo (1940) on the basis of 238 cases of postoperative myxedema followed at the Mayo Clinic, found that the estimated amount of thyroid tissue left at the time of operation was approximately 27 per cent of a normal lobe on either side in cases in which appreciable thyroiditis was not present. In cases of thyroiditis, the amount left was approximately 31 per cent of a normal lobe on either side. These data prove that even a considerable amount of active thyroid does not prevent the development of hypothyroidism in human beings. Man seems to stand alone in showing severe deficiency symptoms after removal of the thyroid gland in later life. It is difficult to understand why man should be more dependent on the thyroid in later life than other mammals. According to Bolk (1921), the essential character of the human body is a survival of fetal conditions. This persistence of fetal conditions is the result of a retardation or suppression of the development of certain general characters in Primates. The rate of development in man is retarded, with the consequence that the infantile or puerile phases of his life are prolonged. It may well be that the need of the adult human for thyroid hormone reflects this general retardation of development characteristic for the species.

CHAPTER VIII

Conclusion

IN CONCLUDING we wish to recapitulate some findings which seem of general interest to the biologist.

Radioactive iodine (I^{131}) is stored in the endostyle of the ammocoetes larva but not in that of lower chordates. These experiments have furnished proof "that the endostyle of ammocoetes is the most primitive thyroid mechanism which possesses a chemically functional analogy with the follicular type of gland so characteristic in adults of all craniates" (Leach, 1946).

In the thyroid region of amphibian larvae storage of iodine begins very early in life. This has been shown by radioautographs of tadpoles of the frog, *Hyla regilla*, cultured in medium containing I^{131} (Gorbman and Evans, 1941a).

In mammals the onset of thyroid function was determined by subcutaneous injection of radioactive iodine (I^{131}) into pregnant rats. Iodine storage could only be demonstrated toward the end of fetal life. Iodine accumulation is initiated on the eighteenth or nineteenth day of fetal life in the Long-Evans strain of rats (Gorbman and Evans, 1941b). Definite histological features could be correlated with the ability to store iodine. Cells which were previously uniformly arranged in columns begin to arrange themselves into follicles. This work confirms previous histological studies. Kull (1926) had shown that follicle formation takes place with an almost explosive unfolding in the thyroid of the albino rat between the

eighteenth and twenty-first days of fetal life. The duration of the fetal life in the rat is 21 days and apparently in this species functional activity of the thyroid is delayed until nearly the end of fetal life.

No general rule can be made from these experiments on rats as to the onset of thyroid activity during the intrauterine life of other mammals. It has been shown that follicle and colloid formation takes place in the thyroid of the pig in a much earlier stage of fetal life than in the rat. Extracts from pig embryos just showing follicle and colloid formation are biologically active. They stimulate metamorphosis in the hypophysectomized tadpole (Rumph and Smith, 1926).

In the human embryo, the thyroid is differentiated histologically at the end of the third month of fetal life. If human thyroid is transplanted into tadpoles of the common toad, *Bufo vulgaris*, at this stage, metamorphosis is induced (Schulze, 1930). These findings have recently been corroborated by studies using radioactive iodine (I^{131}). The human fetal thyroid does not collect radioactive iodine administered to the mother in the first 12 weeks of intrauterine life. Increasing amounts of iodine are collected by the thyroid of the human embryo after the 14th week (Chapman *et al.*, 1948).

The mechanism involved in the synthesis of thyroid hormone seems to be identical throughout the vertebrate phylum. This is not only proven by the similar effect of the administration of antithyroid drugs in fish, amphibia, birds and mammals (Goldsmith, 1949), but also by the finding that the ratio of thyroxin iodine to total iodine in the gland remains fairly constant from species to species (Wolff and Chaikoff, 1947). The values for thyroxin iodine expressed as a percentage of total iodine are within the range of 25 to 32. These values were based on the

chemical analysis of thyroid tissue of 11 vertebrate species· one fish, one reptile, two birds and seven mammals.

Little is known about the levels of protein-bound "hormonal" iodine in various species. The values obtained for protein-bound iodine of plasma of dog, rat, mouse and domestic fowl were found to be quite similar (3 to 4 micrograms per 100 ml.). The amounts contained in human plasma were significantly higher (5 to 8 micrograms per 100 ml.) (Taurog and Chaikoff, 1946).

Bibliography

Abderhalden, E., and Wertheimer, E.: Beziehungen des Lebensalters zur Thyroxinwirkung. *Ztschr. f. ges. exper. Med.*, *68*:1-19, 1929.

Abelin, I., and Scheinfinkel, N.: Gaswechsel und Metamorphose von Amphibienlarven nach Verfutterung von Schilddruse oder von jodhaltigen Substanzen. *Arch. f. d. ges. Physiol.*, *198*:151-163, 1923.

Adams, A., Richards, L., and Kuder, A.: The relation of the thyroid and pituitary gland to moulting in *Triturus viridescens*. *Science*, 72:323-324, 1930

Adams, A. E., and Bull, A. L.: Antithyroid drugs in chick embryos. *Anat. Rec.*, *104*:421-444, 1949.

Albright, F.: The parathyroids. Physiology and therapeutics. *J.A.M.A.*, *117*:527-533, 1941.

Allen, B.: The results of thyroid removal in the larvae of *Rana pipiens*. *J Exper. Zool.*, *24*:445-498, 1917.

Andik, I., Bologh, L., Donhoffer, S, and Mestyan, G.: The thyroxin sensitivity of normal and thyroidectomized rats. *Experientia (Basel)*, *5*:211-213, 1949

Andrews, F. N, and Schnetzler, E. E.: The effect of feeding thiouracil to hens upon the thyroid gland of chicks *Endocrinology*, *37*:382-384, 1945.

Aranow, H., Jr., Englf, E T., and Sperry, W. M.: Some effects of the administration of thiouracil to monkeys. *Endocrinology*, *38*:331-336, 1946.

Asimoff, G.: Bedingte Reflexe bei thyroidektomierten Tieren. *Arch f d. ges. Physiol.*, *220* 350-355, 1928.

Astwood, E. B., Bissel, A., and Hughes, A. M.: Inhibition of the endocrine function of the chick thyroid. *Federation Proc.*, *3*:2, 1944.

———, Sullivan, J., Bissel, A., and Tyslowitz, R.: Action of certain sulfonamides and of thiourea upon the function of the thyroid gland of the rat. *Endocrinology, 32:*210-225, 1943.

Babak, E.: Einige Gedanken uber die Beziehung der Metamorphose bei den Amphibien zur inneren Sekretion. *Zentralbl. f. Physiol., 27:*536-541, 1913.

Baker, B. L: Study of parathyroid glands of normal and hypophysectomized monkey *(Macaca mulata). Anat. Rec., 83:* 47-73, 1942.

Barker, S. P., Kiely, C. E., Jr., and Lipner, H. J.: Metabolic effects of thyroxin injected into normal, thiouracil-treated and thyroidectomized rats. *Endocrinology, 45:*624-627, 1949.

Basinger, H. R.: The control of experimental cretinism. *Arch. int. Med., 17:*260-278, 1916.

Baumann, R.: Vom congenitalen Myxoedem zum kretinistischen Zwergwuchs der Ferkel *(Dickhals). Wien. tierarztl. Monatschr., 35:*316-324, 1948.

Becks, A., Ray, R. D., Simpson, M. E., and Evans, H. M.: Effect of thyroxin and the anterior pituitary growth hormone on endochondral ossification. *Arch. Path., 34:*334-351, 1942.

Belasco, I. J., and Murlin, J. R.: Effect of thyroxin and thyrotropic hormone on basal metabolism and thyroid tissue respiration of rats of various ages. *Endocrinology, 28:*145-152, 1941.

Berkeley, W. H., and Beebe, S. P.: A contribution to the physiology and chemistry of the parathyroid gland. *J. Med. Research, 20:*149-173, 1909.

Biedl, A.: *Innere Sekretion,* 2nd edition. Berlin and Wien, Urban and Schwarzenberg, 1913.

Binswanger, F.: Studien zur Physiologie der Schilddruse. III. Schilddruse und Wachstum *(Studien am Hund). Endokrinologie, 17:*150-161, 1936.

Blivaiss, B.. *Interrelations of thyroid and gonad in development of plumage and other sex characters in Brown Leghorn Roosters Physiol. Zool., 20.*67-107, 1947.

Bodansky, A., Blair, J. E., and Jaffe, H. L.: Experimental hyperparathyroidism in guinea pigs leading to osteitis fibrosa. *J. Biol. Chem.*, *88*:629-647, 1930.

———, and Jaffe, H. L.: Parathormone dosage and serum calcium and phosphorus in experimental chronic hyperparathyroidism. *J. Exper. Med.*, *53*.591-604, 1931.

Bodansky, M., and Duff, V. B.· Age as a factor in the resistance of the Albino rat to thyroxin with further observations on the creatine content of tissues in experimental hyperthyroidism. *J. Exper. Med.*, *53*:591-604, 1931.

Bolk, L.. The part played by the endocrine glands in the evolution of man *Lancet*, *201*:588-592, 1921.

Brand, T. v., Holtz, F., and Putschar, W.. Vergleichende pharmakologische Untersuchungen uber Calcinosefaktor und Nebenschilddrusenhormon *Arch. exper. Path. u. Pharmakol.*, *167*:113-145, 1932.

Brody, S.. *Bioenergetics and Growth.* New York, Reinhold, 1945.

———, and Frankenbach, R. F.: Growth and development. Age changes in size, energy metabolism and cardio-respiratory activities of thyroidectomized cattle. *Missouri Agr. Exper Station Research Bull.*, *349*:1-11, 1942.

Brolin, S. E A study of the structural and hormonal relations of the pituitary body of rats exposed to cold. *Acta anat Supplement 3*, *2*:1-165, 1945.

———· The size of the pituitary body and its lobes after thyroidectomy and after parathyroidectomy in adult male and female rats *Acta endocrinol.*, *1*:304-318, 1948.

Bulbring, E. Über die Beziehungen zwischen Epithelkorperchen, Calciumstoffwechsel und Knochenwachstum. *Arch. exper Path. u. Pharmakol*, *162*:209-248, 1931.

Caridroit, F.. Effets de la thyroxine sur le plumage du chapon Leghorn doré au seuil de feminisation *Compt rend Soc. de Biol.*, *134*:5-7, 1940.

———, and Regnier, V.: De l'influence de la sécrétion thyroidienne sur la réceptivité a l'hormone mâle de la crête du chapon. *Rev Scient.* (Paris), *79*:309-315, 1941.

Carlson, A. J.: The parathyroids and pregnancy. *Proc. Soc. Exper. Biol. & Med*, *10*:183-184, 1913.

———, AND WOELFEL, A.: On the internal secretion of the thyroid gland. *Am. J. Physiol.*, *26*:32-67, 1910.

CARNES, W. H., OSEBOLD, J., AND STOERCK, H. C.: Parathyroid function in the hypophysectomized rat. *J. Biol. Chem.*, *139*:188-192, 1943.

CAYLOR, H. D., AND SCHLOTTHAUER, C. F.: The influence of diet in the development of myxedema in thyroidectomized pigs. *Am. J. Physiol.*, *89*:596-600, 1929.

CHAMPY, C.: L'action de l'extrait thyroidien sur la multiplication cellulaire. *Arch. de Morphol. gén. et exp.*, *4*:1-58, 1922.

CHANDLER, S. B.: Relation of parathyroidectomy to estrus, pregnancy and lactation in the albino rat. *Anat. Rec.*, *53*: 105-120, 1932.

CHAPMAN, E. M., CORNER, G. W., JR., ROBINSON, D., AND EVANS, R. D.: The collection of radioactive iodine by the human fetal thyroid. *J. Clin. Endocrinol.*, *8*:717-720, 1948.

COLLIP, J. B.: The extraction of a parathyroid hormone which will prevent or control parathyroid tetany and which regulates the level of blood calcium. *J. Biol. Chem.*, *63*:395-438, 1925.

———, CLARK, E. P., AND SCOTT, J. W.: The effect of parathyroid hormone on normal animals. *J. Biol. Chem.*, *63*:439-460, 1925.

CUTTING, C. C., AND TAINTER, M. L.: Comparative effects of dinitrophenol and thyroxin on tadpole metamorphosis. *Proc. Soc. Exper. Biol. & Med.*, *31*:97-100, 1933.

DANOWSKI, T. S., MAN, E. B., AND WINKLER, A. W.: Tolerance of normal, of thyroidectomized and of thiourea or thiouracil treated dogs to oral desiccated thyroid and to intravenous thyroxine. *Endocrinology*, *38*:230-237, 1946.

DEMPSEY, E. W., AND ASTWOOD, E. B.: Determination of the rate of thyroid hormone secretion at various environmental temperatures. *Endocrinology*, *32*:509-518, 1943.

———, GREEP, R. O., AND DEANE, H. W.: Changes in the distribution and concentration of alkaline phosphatases in tis- [illegible] gonadectomy, and [illegible] *44*.88-103, 1949.

D[illegible] *Munchen. tierärztl. Wchnschr*, 69-74, 1944.

Doyon, M., and Jouty, A.: Ablation des parathyroides chez l'oiseau. *Compt. rend. Soc. de biol.*, 56:11-12, 1904.

Duerst, J. U.: *Die Ursachen der Entstehung des Kropfes.* Bern, Huber, 1941.

Drzewicki, S.: La Metamorphose partielle de la peau des têtards de *Pelobates fuscus* Laur. sur l'influence de quantités minimales de substance de la glande thyroide. *Compt. rend. Soc. de biol.*, 90:1364-1366, 1924.

Eggert, B.: Über die histologischen und physiologischen Beziehungen zwischen Schilddruse und Hautung bei den einheimischen Eidechsen. *Zool. Anz.*, 105:1-9, 1933.

Eiselsberg, A. v.: Wachstumsstorungen bei Tieren mit frühzeitiger Schilddrusenextirpation. *Arch. f. klin. Chir.*, 49:207-234, 1895.

Engle, E. T., and Aranow, H., Jr.: Hyperplasia of the thyroid gland of rhesus monkeys after thiouracil treatment. *Endocrinology*, 38:325-330, 1946.

Erdheim, J.: Über die Dentinverkalkung im Nagezahn bei der Epithelkorperchentransplantation. *Frankf. Ztschr. f. Path.*, 7:238-248, 1911.

Ershoff, B. H.: Effects of thiouracil feeding on resistance to low environmental temperature. *Endocrinology*, 43:36-39, 1948.

Etkin, W.: The phenomena of anuran metamorphosis. II Oxygen consumption during normal metamorphosis. *Physiol. Zool.*, 7:129-148, 1934.

Fasold, H., and Heidemann, E. R.: Über die Gelbfarbung der Milch thyreopriver Ziegen. *Ztschr. f. d. ges. exper. Med.*, 92:53-56, 1933.

Fleischmann, W.: Zur Frage der Beeinflussung Wirbelloser durch Wirbeltierinkrete. *Arch. f. d. ges. Physiol.*, 221:591-593, 1929.

———: Effect of thyroxin on estrogen-induced changes in fowl. *Federation Proc.*, 5:28, 1946.

———: Comparative physiology of the thyroid hormone. *Quart. Rev. Biol.*, 22:119-140, 1947.

———, and Fried, I.: Studies on the mechanism of the hypercholesterolemia and hypercalcemia induced by estrogen in immature chicks. *Endocrinology*, 36:406-415, 1945.

———, AND KANN, S.: Untersuchungen über die Beziehungen zwischen dem Schilddrüsenhormon und dem Vitamin A. *Wien. klin. Wchnschr.*, *49:*1488-1489, 1937.

———, AND SHUMACKER, H. B., JR.: The relationship between serum cholesterol and total body cholesterol in experimental hyper and hypometabolism. *Bull. Johns Hopkins Hosp.*, *71:* 175-183, 1942.

———, ———, AND STRAUS, W. L., JR.: Influence of age on the effects of thyroidectomy in the rhesus monkey. *Endocrinology*, *32:* 238-246, 1943.

———, ———, AND WILKINS, L.: The effect of thyroidectomy on serum cholesterol and basal metabolic rate in the rabbit. *Am. J. Physiol.*, *131:*317-324, 1940.

———, STUBBS, J. L., AND MCSHANE, W. P.: Effect of alpha naphthylthiourea (ANTU) on serum cholesterol in thyroidectomized dogs. *Proc. Soc. Exper. Biol. & Med.*, *70:*246-248, 1949.

FONTAINE, M., AND OLIVEREAU, M.: La glande thyroïde du saumon atlantique (*Salmo salar L.*) au cours de sa vie en eau douce. *Compt. rend. Acad. d. sc.*, *224:*1660-1672, 1947.

FORSYTH, D.: The comparative anatomy, gross and minute of the thyroids and parathyroids in mammals and birds. *J. Anat. Physiol.*, *42:*141-168, 302-318, 1908.

GANTT, W. H., AND FLEISCHMANN, W.: Effect of thyroid therapy on the conditional reflex function in hypothyroidism. *Am. J. Psychiat.*, *104:*673-681, 1948.

GHIDONI, M. B.: Effect of thyroid inhibitors upon tail regeneration in the tadpole. *Growth*, *12:*181-202, 1948.

GILLIGAN, D. R., VOLK, M. C., DAVIS, D. D., AND BLUMGART, H. L.: Therapeutic effect of total ablation of normal thyroid on congestive heart failure and angina pectoris. *Arch. Int. Med.*, *54:*746-757, 1934.

GLOCK, G. E.. Effects of the administration of thiouracil to dogs. *J. Endocrinol.*, *6:*6-13, 1949.

GOLDBERG, R. C., AND CHAIKOFF, I. L.: A simplified procedure for thyroidectomy of the new-born rat without concomitant parathyroidectomy. *Endocrinology*, *45:*64-70, 1949.

GOLDMANN, H.: Experimentelle Tetaniekatarakt. *Arch. f. Ophth.*, *122:*146-197, 1929.

GOLDSMITH, E. D.: Phylogeny of the thyroid: Descriptive and experimental. *Ann. New York Acad. Sc.*, *50*:283-316, 1949.

———, NIGRELLI, R. F., GORDON, A. S., CHARIPPER, H. A., AND GORDON, M.: Effect of thiourea upon fish development. *Endocrinology*, *35*:132-134, 1944.

GORBMAN, A.: Identity of an iodine-storing tissue in an Ascidian. *Science*, *94*:192, 1941.

———: Effects of radiotoxic dosages of I[131] upon thyroid and contiguous tissues in mice. *Proc. Soc. Exper. Biol. & Med.*, *66*:212-213, 1947.

———, AND CREASER, C. W.: Accumulation of radioactive iodine by the endostyle of larval lampreys and the problem of homology of the thyroid. *J. Exper. Zool.*, *89*:391-405, 1942.

———, AND EVANS, H. M.: Correlation of histological differentiation with beginning function of developing thyroid gland of frog. *Proc. Soc. Exper. Biol. & Med.*, *47*:103-106, 1941a.

———, AND ———: Time of beginning of function in the thyroid gland of fetal rats. *Anat. Rec.*, *81*:95-96, 1941b.

GORDON, A. S., GOLDSMITH, E. D., AND CHARIPPER, H. A.: Effect of thiourea on the development of the amphibian. *Nature*, *152*:504-505, 1943.

GRAFFLIN, A. L.: Further observations upon parathyroid gland of Virginia deer, in specimens taken throughout the year. *Endocrinology*, *30*:571-573, 1942.

GRIMMER, W.: Beitrage zur Kenntnis der Milch schilddrusenloser Ziegen. *Biochem. Ztschr.*, *88*:43-52, 1918.

GROLLMAN, A.: *Essentials of Endocrinology*. Second edition. Philadelphia, Lippincott, 1947.

GUDERNATSCH, J. F.: Feeding experiments on tadpoles. I. The influence of specific organs given as food on growth and differentiation. A contribution to the knowledge of organs with internal secretions. *Arch. Entwmech. Org.*, *35*:457-501, 1913.

HAFFNER, F.: Pharmakologische Untersuchungen mit einem deutschen Thyroxin. *Klin. Wchnschr.*, *6*:1932-1935, 1927.

HAGEN, F. v.: Die wichtigsten Erkrankungen des Flussaals (*Anguilla vulgaris*). *Zool. Jahrb.* (Anat.), *61*:467-538, 1936.

HALPENNY, J., AND GUNN, J. A.: Note on the extirpation of the thyroid gland in monkeys. *Quart. J. Exper. Physiol.*, *4*:237-241, 1911.

HAMILTON, C. F., ALBERT, A., AND POWER, M. H.: Bio-assay of calorigenic substances using tadpoles of *Xenopus laevis*. *Endocrinology*, *43*:406-414, 1948.

HAMMETT, F. S.: Studies of the thyroid apparatus. XLVIII. Age, sex, weight and season as lethal factors in conditions of parathyroid and thyroid deficiency. *Endocrinology*, *11*:117-124, 1927.

HARMS, J. W.: Die Realisation von Genen und die consecutive Adaption. *Ztschr. wiss. Zool.*, *133*:211-297, 1929.

HARRIS, P. N., ANDERSON, R. C., AND CHEN, K. K.: The action of alloxan, senecionine, sulfadiazine and thiouracil in the hamster. *J. Pharmacol. Exper. Therap.*, *87*:382-386, 1946.

HARRISON, H. E., AND HARRISON, H. C.: The renal excretion of inorganic phosphate in relation to the action of vitamin D and parathyroid hormone. *J. Clin. Investigation*, *20*:47-55, 1941.

HELFF, O. M.: The oxygen consumption of thyroid and diiodotyrosine-fed tadpoles. *Proc. Soc. Exper. Biol. & Med.*, *21*:34-39, 1923.

———: Studies on amphibian metamorphosis. II. The oxygen consumption of tadpoles undergoing metamorphosis following treatment with thyroid and diiodotyrosine. *J. Exper. Zool.*, *45*:69-93, 1926.

HENSCHEL, H., AND STEUBER, M.: Über die Bedeutung der Schilddruse fur den Stoffwechsel der Amphibien. *Arch. f. exper. Path. u. Pharmakol.*, *160*:401-427, 1931.

HESSE, E., VONDERLINN, H., AND ZEPPMEISEL, L.: Entgiftung des. Schilddrüsenhormons. *Arch. f. exper. Path. u. Pharmakol.*, *173*:192-204, 1933.

HOFMEISTER, F.: Experimentelle Untersuchungen uber die Folgen des Schilddrusenverlustes. *Beitr. z. Klin. Chir.*, *11*: 441-523, 1894.

HOGBEN, L.: *The comparative physiology of internal secretion.* Cambridge, England, Cambridge University Press, 1929

HORSLEY, V. A.: Further researches into the function of the thyroid gland and into the pathological state produced by the removal of the same. *Proc. Roy. Soc. London, 40*:6-9, 1886.

HOSKINS, M. M.: The relation of the thyroid to certain stages of metamorphosis in frog larvae. *Anat. Rec*, *23*:21, 1922.

HOUSSAY, B. A., AND HUG, H.: La thyroidectomie chez les chevaux. *Compt. Rend. Soc. de biol.*, *83*:1242-1243, 1920.

HOWARD, J. E.: Metabolism of calcium and phosphorus in bone. *Bull. New York Acad. Med.*, 27:24-41, 1951.

HUEPER, W.: Metastatic calcifications in the organs of the dog after injections of parathyroid extract. *Arch. Path., 3:* 14-25, 1927.

HUGHES, A. M.· Cretinism in rats induced by thiouracil. *Endocrinology*, *34* 69-76, 1944.

———, AND ASTWOOD, E. B.: Inhibition of metamorphosis in tadpoles by thiouracil. *Endocrinology*, *34*·138-139, 1944.

HUNTER, M. W., AND SAWIN, P. B.: The effects of thyroidectomy on the skull of the domestic rabbit. *Am. J. Anat.*, *71:* 417-450, 1942.

HYMAN, L H: *Comparative anatomy of vertebrates.* 2nd ed. Chicago, Univ. of Chicago Press, 1942.

ILJIN, N A . Farbenveranderungen der Russen-kaninchen und einer siamesischen Katze, hervorgerufen durch Schilddrusenwirkung. *Arch. Entwmech. Org*, *125*:306-340, 1932.

JAAP, R. G: Pigmentation and growth rate in gray breast feathers of adult Mallard drakes. *Proc. Soc. Exper. Biol. & Med*, *31*:630-634, 1934.

JAILER, J. W., SPERRY, W. M., ENGLE, E T., AND SMELSER, G · Experimental hypothyroidism in the monkey. *Endocrinology*, *35*:27-37, 1944

JONES, G E. A., DELFS, E., AND FOOTE, E. C.: The effect of thiouracil hypothyroidism on reproduction in the rat. *Endocrinology*, *38*.337-344, 1946.

JUHN, M Feather pigmentation and leucosis in the brown Leghorn *Anat. Rec.*, *84*·531, 1942.

——— Effect of thiouracil on the plumage of the brown Leghor

———

Leghor

KISHI, K.: Beiträge zur Physiologie der Schilddruse. *Arch path. Anat., 176*:260-314, 1904.

KOHN, A.: Studien uber Schilddruse. *Arch. f. mikr. Anat., 44*: 366-422, 1895.

KONEFF, A. A., NICHOLS, C. W., WOLFF, J., AND CHAIKOFF, I. L.: The fetal bovine thyroid. Morphogenesis as related to iodine accumulation. *Endocrinology, 45*:242-249, 1949.

KOZELKA, F. L., HART, E. B., AND BOHSTEDT, G: Growth, reproduction, and lactation in the absence of the parathyroid glands. *J. Biol. Chem., 100*:715-729, 1933.

KUHN, O.: Schilddrusenfunktion und Neotenie bei Urodelen. *Biol. Zentralbl., 45*:483-495, 1925.

KULL, H. A.: The late embryonic development of the thyroid gland of the albino rat. *Anat. Rec., 32*:133-141, 1926.

LANDAUER, W.: Thyrogenous dwarfism (myxedema infantile) in the domestic fowl. *Am. J. Anat., 43*:1-49, 1927.

LARSON, E., AND ELKOURIE, L. A.: Tetany and blood calcium after thyroparathyroidectomy in the goat. *Proc. Soc. Exper. Biol. & Med., 26*:210-213, 1928.

LEACH, W. J.: Oxygen consumption of lampreys, with special reference to metamorphosis and phylogenetic position. *Physiol. Zool., 19*:365-374, 1946.

LEBRETON, E., AND SCHAEFFER, G.: Action de la thyroxine sur la valeur du métabolisme basal du lapin au cours de la croissance. *Compt. Rend. Soc. de biol., 118*:448-450, 1935.

LIDDELL, H. S., AND SIMPSON, E. D.: A preliminary study of conditioned motor reflexes in thyroidectomized sheep. *Proc. Soc. Exper. Biol. & Med., 23*:720-722, 1926.

LIEGEOIS, F., AND DERIVAUX, J.: Hyperparathyroïdie d'origine alimentaire. *Compt. rend. Soc. de biol., 143*:128-129, 1949a.

———, AND ———: Nature de l'hypertrophie parathyroïdien due à l'hyperphosphorose alimentaire chez le porc. *Compt. rend. Soc. de biol., 143*:587-588, 1949b.

LILLIE, F. R., AND JUHN, M.: The physiology of development of feathers. I. Growth-rate and patterns in the individual feather. *Physiol. Zool., 5*:124-184, 1932.

MACCALLUM, W. G., AND VOEGTLIN, C.: On the relation of tetany to the parathyroid glands and to calcium metabolism. *J. Exper. Med., 11*:118-151, 1909.

MacKenzie, C. G., and MacKenzie, J. B.: Effect of sulfonamides and thioureas on the thyroid gland and basal metabolism. *Endocrinology, 32*:185-209, 1943.

———, ———, and McCollum, E. V.: Effect of sulfanylguanidine on thyroid of rat. *Science, 94*:518-519, 1941.

Mahrer, M. E., and Hogan, A. G.: Effect of thiouracil on growing swine. *Proc. Soc. Exper. Biol. & Med., 60*:211-212, 1946.

Marine, D.: Physiology and Principal Interrelations of the thyroid gland. *Bull New York Acad. Med., 15*:790-804, 1939.

———, and Lenhart, C. H.: Observations and experiments on the so-called thyroid carcinoma of brook trout *(Salvelinus fontinalis)* and its relation to ordinary goitre. *J. Exper. Med*, *12*:311-337, 1910.

———, and ———: Further observations and experiments on the so-called thyroid carcinoma of the brook trout *(Salvelinus fontinalis)* and its relation of endemic goitre. *J. Exper. Med., 13*:455-473, 1911.

———, and ———. The influence of glands with internal secretions on the respiratory exchange. I. Effect of subcutaneous injection of adrenalin on normal and thyroidectomized rabbits. *Am. J. Physiol., 54*:248-260, 1920

Marston, H. R., and Pierce, A. W. The effects following thyroidectomy in merino sheep. *Austral J. Exper. Biol. & m. Sc., 10*.203-213, 1932

Marvin, H. N, and Smith, G. C.. Technique for thyroidectomy in the pigeon and the early effect of thyroid removal on heat production. *Endocrinology, 32*:87-91, 1943.

Matthews, S A, and Smith, D C. Concentration of radioactive iodine by the thyroid gland of the parrot fish. *Sparisoma sp. Am. J. Physiol., 153*·222-225, 1948.

Mautner, H: Posology in pediatrics. *J. Pediat., 157*:65-83, 1941

Mayer, E. Inhibition of beagle puppies by propylthiouracil without disturbance of growth or health *Endocrinology, 40*:165-181, 1947.

McDonald, M. R., Riddle, O., and Smith, G. C Action of thyroxin on estrogen-induced changes in blood chemistry and endosteal bone *Endocrinology, 37*:23-28, 1945.

McGinty, D. A., and Wilson, L. M.: Comparative activity of thiouracil and other antithyroid compounds in the rhesus monkey. *Endocrinology, 44*:546-554, 1949.

McLean, F. C., Barnes, B. O., and Hastings, A. B.: The relation of the parathyroid hormone to the state of calcium in the blood. *Am. J. Physiol., 113*:141-149, 1935.

Means, J. H.: *The Thyroid and its diseases.* Second edition. Philadelphia, Lippincott, 1948.

———, and Richardson, E. P.: *Diagnosis and treatment of diseases of the thyroid.* New York, Oxford, 1938.

Mellish, C. H., and Meyer, R. K.: The effects of various gonadotropic substances and of thyroxin on the ovaries of horned lizards *(Phrynosoma cornutum). Anat. Rec., 69*:179-189, 1934.

Meyer, A. E., and Ransom, G. V.: The metabolism of rats after thyroidectomy or during thiouracil treatment, and the effect of thyroid feeding. *Endocrinology, 36*:259-265, 1945.

Mixner, J. P., Reineke, E. P., and Turner, C. W.: Effect of thiouracil and thiourea on the thyroid gland of the chick. *Endocrinology, 34*:168-174, 1944.

Monroe, R. A., and Turner, C. W.: Metabolism of Thyroxine in the Goat. *Am. J. Physiol., 154*:1-5, 1948.

Moussu, M.: Sur la fonction thyroidienne Crétinisme experimental sous les deux formes typiques. *Compt. rend. Soc. de biol., 44*:972-979, 1892.

Munk, H.. Zur Lehre von der Schilddruse. *Arch. path. Anat., 150*:271-305, 1897.

Nagel, A. L.. Beobachtungen bei der Metamorphose Schilddrusen gefutterter Axolotl. *Arch. f. exper. Path. u. Pharmakol., 120*:1-15, 1927.

Neuweiler, W.: Versuche uber die Beeinflussung der Genitalfunktion der weibliche Ratte durch Epithelkorperchenextrakt. *Zentralbl. f. Gynäk., 57*:456-458, 1933.

Noble, G. K, and Bradley, H. T.: The relation of the thyroid and the hypophysis to the molting process in the lizard, *Hemidactylus Crookii Biol. Bull., 64*:289-298, 1933.

Parkes, A. S., and Selye, H.: The endocrine system and plumage types. *J. Genetics, 34*:297-306, 1937.

PETERSEN, W. E., SPIELMAN, A., POMEROY, B. S., AND BOYD, W. L.: Effect of thyroidectomy upon sexual behavior of the male bovine. *Proc. Soc. Exper. Biol. & Med.*, *46*:16-17, 1941.

PICK, E. P., AND PINELES, F.: Untersuchungen über die physiologisch wirksame Substanz der Schilddruse. *Z. exp. Path.*, 7:518-531, 1909.

RAAB, W.: Thiouracil treatment of angina pectoris. *J. Amer. Med. Ass.*, *128*:249-256, 1945.

RALSTON, N. P., COWSERT, W. C., RAGSDALE, A. C., HERMAN, H. A., AND TURNER, C. W.: Yield and composition of the milk of dairy cows and goats as influenced by thyroxine. *Missouri Agr. Exper. Sta. Research*, *317*:75, 1940.

RICHTER, C. P., AND CLISBY, K. H.: Toxic effects of bitter tasting phenylthiocarbamide. *Arch. Path.*, *33*:46-57, 1942.

RIDDLE, O., AND McDONALD, M. R.: The partition of plasma calcium and inorganic phosphorus in estrogen-treated normal and parathyroidectomized pigeons. *Encrinology*, *36*: 48-52, 1945.

———, RAUCH, V. M., AND SMITH, G.: Action of estrogen on plasma calcium and endosteal bone formation in parathyroidectomized pigeons. *Endocrinology*, *36*:41-47, 1945.

ROBERTSON, O. H.: The occurrence of increased activity of the thyroid gland in Rainbow trout at the time of transformation from parr to silvery smolt. *Physiol. Zool.*, *21*: 282-295, 1948

ROELANDTS, H., AND DE WAELE, H.: Antagonisme entre thymus et thyroide. *Ann. de physiol.*, *12*:784-786, 1936.

ROLIC, T.: Relative activity of thyroids of axolotl and amblystoma *Zh eksp. Biol. Med.* (Moscow), *8*:60-72, 1927.

ROOT, R. W., AND ETKIN, W.: Effect of thyroxine on oxygen consumption of the toadfish. *Proc. Soc. Exper. Biol & Med*, 37 174-175, 1937

RUMPH, P., AND SMITH, P. E. The first occurrence of secretory products and of a specific structural differentiation in the thyroid and anterior pituitary during the development of the pig foetus *Anat. Rec*, 33.289-299, 1926.

SADHU, P. D., AND BRODY, S.: Excess vitamin A ingestion, thyroid size, and energy metabolism. *Am. J. Physiol.*, *149*:400-403, 1947.

Salmon, T. N.: The effect on the growth rate of thyro-paratryroidectomy in newborn rats and of the subsequent administration of thyroid, parathyroid and anterior hypophysis. *Endocrinology, 23:*446-457, 1938.

Schulze, W.: Der Einfluss der inkretorischen Drüsen und des Nervensystems auf Wachstum und Differenzierung. *Handb. norm. path. Physiol.,* Berlin, Springer, *16 (1):*697-806, 1930.

Scow, R. O., Simpson, M. E., Asling, C. W., Li, C. H., and Evans, H. M.: Response by the rat thyro-parathyroidectomized at birth to growth hormone and to thyroxin given separately or in combination. *Anat. Rec., 104:*445-464, 1949.

Siler, K. A.: The cytological changes in the hypophysis cerebri of the garter snake *(Thamnophis radix)* following thyroidectomy. *J. Morphol., 59:*603-619, 1936.

Simpson, S.: Age as a factor in the effects which follow thyroidectomy and parathyroidectomy in the sheep. *Quart. J. Exper. Physiol., 6:*119-145, 1913.

———: The effect of thyroidectomy on growth in the sheep and goat as indicated by body weight. *Quart. J. Exper. Physiol., 14:*161-184, 1924.

———: Effects of thyroidectomy on the cutaneous system in the sheep and goat. *Quart. J. Exper. Physiol., 14:*185-190, 1924.

Sklower, A.: Das inkretorische System im Lebenszyklus der Frösche. *Ztschr. vergl. Physiol, 2:*474-523, 1925.

———: *Die Bedeutung der Schilddruse fur die Metamorphose der Aales und der Plattfische. Fortschr. d. Neurol., Psychiat., 6:*435-436, 1930.

Slowikowska, S.. Recherches experimentales sur le role de la glande thyroide dans la métamorphose des batraciens. *Compt. rend. Soc. de Biol., 89:*1396-1398, 1923

Smith, D. C., and Everett, G. M.: The effect of thyroid hormone on growth rate, time of sexual differentiation and oxgen consumption of the fish. *Lebistes reticulatus. J. Exper Zool., 94:*229-240, 1943.

Smith, E. E., and McLean, F. C.: Effect of hyperthyroidism upon growth and chemical composition of bone. *Endocrinology, 23:*546-552, 1938.

Smith, G. E.: Fetal athyrosis. *J. Biol. Chem., 29:*215-225, 1917.

———, AND ———: Further observations upon the functions of the thyroid and parathyroid glands. *J. Physiol., 34:*295-305, 1906.

WAGGENER, R. A.: An experimental study of the parathyroids in the Anura. *J. Exper. Zool., 57:*13-51, 1930.

WILKINS, L.: Epiphyseal dysgenesis associated with hypothyroidism. *Am. J. Dis. Child., 61:*13-34, 1941.

———, AND FLEISCHMANN, W.: The diagnosis of hypothyroidism in childhood. *J.A.M.A., 116:*2459-2465, 1941.

WILSON, W. D., AND MAYO, C. W.: Postoperative myxedema. *Surgery, 7:*117-121, 1940.

WINCHESTER, C. F.: Influence of thyroid on egg production. *Endocrinology, 24:*697-701, 1931.

———, CONAR, C. L., AND DAVIS, G. K.: Thyroid destruction by I^{131} and replacement therapy. *Science, 110:*302-304, 1949.

WOLFF, J., AND CHAIKOFF, I. L.: The relation of thyroxin to total iodine in the thyroid gland. *Endocrinology, 41:*295-298, 1947.

ZALESKY, M., AND WELLS, L. J.: Experimental studies of thyroid, effects of thyroidectomy on reproductive organs in males of an annual breeding ground squirrel. *Anat. Rec., 69:*79-97, 1937.

ZAWADOWSKY, B., AND ROCHLINA, M.: Ueber den Einfluss der experimentellen Hyperthyreoidisierung auf verschiedene Vogelgattungen. *Arch Entwmech. Org., 109:*188-209, 1927.

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